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Possible Role of Cardioaortic Reflexes in Postcoronary Bypass Hypertension

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A study of hemodynamic and humoral characteristics of postcoronary bypass hypertension has been pursued in 85 patients in the immediate postoperative period. Paroxysmal hypertension developed in 69 of these patients. None of the 85 patients had a history of hypertension before operation. Hemodynamic evaluation demonstrated that the increase in blood pressure was associated with an elevation in systemic vascular resistance and a rapid heart rate. The increase in mean arterial pressure correlated significantly with the change in plasma catecholamine levels ($r = 0.50$, $P < 0.05$). There was no significant change in cardiac output. Changes in plasma renin activity showed no correlation with the increase in blood pressure. Average values of plasma renin activity on sequential determinations were not significantly different either in those who remained normotensive or in those who became hypertensive. Similarly, blood volume did not seem to play an important role. Baroreceptor sensitivity appeared blunted in both normotensive and hypertensive patients. The increase in systemic catecholamines associated with the increase in blood pressure suggested a sympathetic overdrive. This was further supported by the control of hypertension in 81 percent of patients by unilateral stellate block. The reduction in pressure consequent to the block was associated with a reduction in systemic vascular resistance ($P < 0.025$). Heart rate slowed slightly but significantly ($P < 0.01$) after stellate block irrespective of the effect on blood pressure whereas cardiac output did not change significantly. The results suggest that postcoronary bypass hypertension could be due to an afferent sympathetic reflex originating from the heart, great vessels or coronary arteries.

Although postcoronary bypass hypertension is now well recognized, its cause is still a subject of debate. The seriousness of the complications that it can precipitate[1–3] mandates the study of its characteristics and pathogenesis to delineate rational therapy or plan effective prevention. In this paper we summarize our continuing experience with the study of its hemodynamic and humoral aspects in 85 patients after coronary bypass surgery.

The evidence gathered to date continues to point to a sympathetic reflex mechanism originating probably from the heart and great vessels. This conclusion, which was suggested by our initial hemodynamic studies,[4] was subsequently substantiated by results of unilateral stellate block.[5] These initial observations were extended to a larger number of patients, and sequential determinations of plasma renin activity and circulating catecholamines have now been added to hemodyamic investigations.

Methods

Study patients: Eighty-five unselected patients, 7 women and 78 men, were studied after coronary bypass surgery. All were known to be normotensive preoperatively. Their ages ranged from 33 to 65 years. Coronary artery disease had been recognized from weeks to years before operations and confirmed in all instances with coronary arteriography. Left ventricular end-diastolic pressure

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(25)

Left Ventricular Function After Valve Replacement

Left Anterior Fascicular Block

Seminar on Myocardial Oxygen Utilization

Karl T. Weber, MD, FACC, Guest Editor

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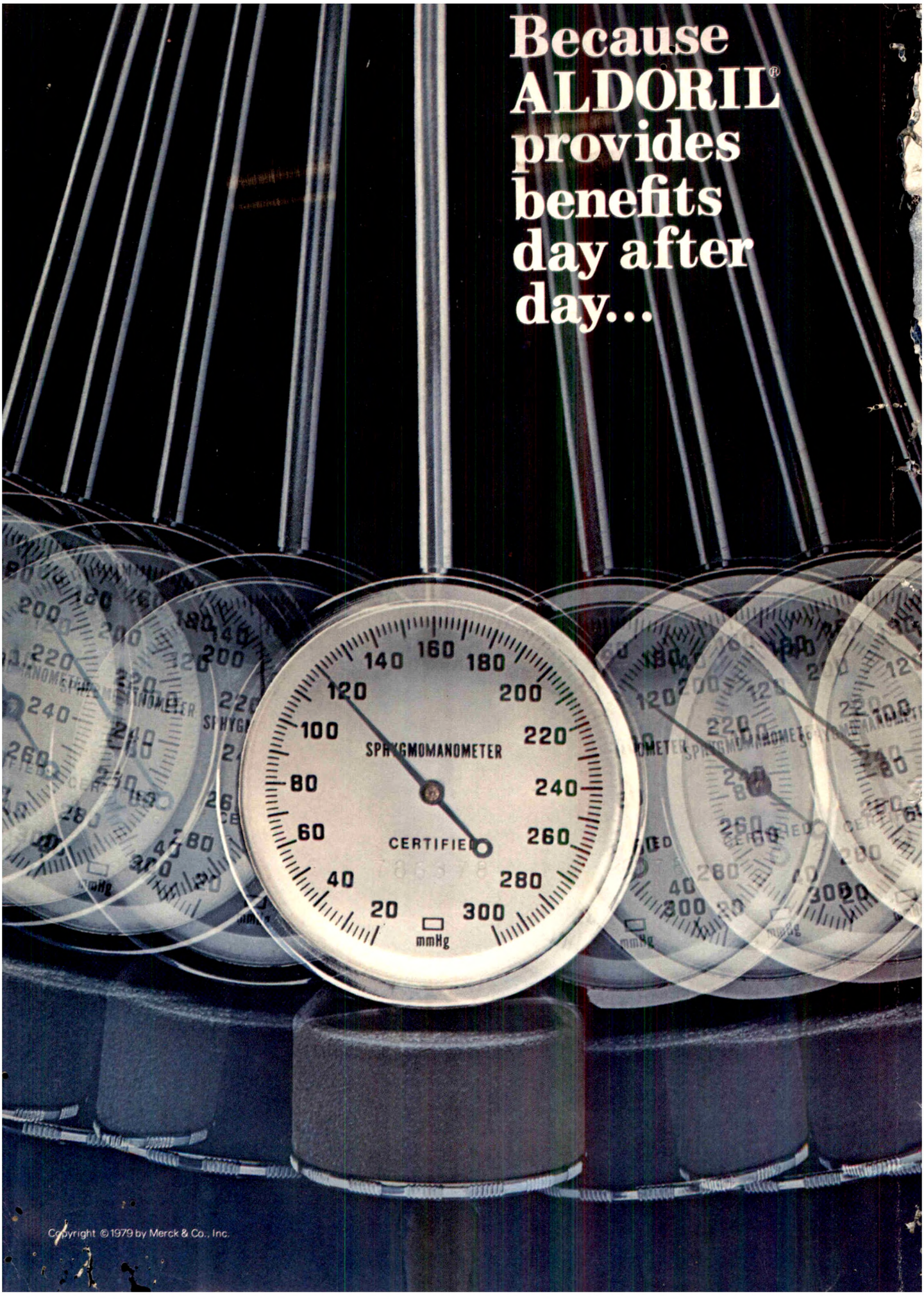

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- **two highly effective complementary agents**

As a fixed combination, ALDORIL is not indicated for initial therapy since hypertension requires therapy titrated to the individual patient. If an available strength of ALDORIL meets the patient's titrated needs, the combination drug may be more convenient in patient management. Therapy should be reevaluated as necessary.

ALDORIL is contraindicated in active hepatic disease; anuria; hypersensitivity to methyldopa or to hydrochlorothiazide or other sulfonamide-derived drugs; if previous methyldopa therapy has been associated with liver disorders. In patients with renal disease, thiazides may precipitate azotemia. Use with caution in patients with severe renal disease or impaired hepatic function.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details, see the brief summary of prescribing information.

For a brief summary of prescribing information, please see following page.

practical benefits

- **effects on daily activities usually minimal**
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- **greater dosage convenience:** a b.i.d. regimen is possible for many patients
- **four dosage strengths:** offer the widest range of dosage strengths available in a combination antihypertensive

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WARNING

This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see **Warnings**); anuria; routine use in an otherwise healthy pregnant woman with or without mild edema; hypersensitivity to methyldopa or to hydrochlorothiazide or other sulfonamide-derived drugs.

Warnings: METHYLDOPA—**It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.**

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within the first three weeks of therapy, sometimes with eosinophilia or abnormalities in one or more liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually within the first two to three months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever, abnormalities in liver function tests, or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, reversible reduction of white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Follow patients carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

HYDROCHLOROTHIAZIDE—Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects may develop in patients with impaired renal function. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. May add to or potentiate action of other antihypertensive drugs; potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity; read circulars for lithium preparations before use of such concomitant therapy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant requires that anticipated benefits be weighed against possible risks.

Methyldopa and thiazides cross the placental barrier and appear in cord blood.

No unusual adverse reactions have been reported in association with the use of methyldopa during pregnancy. Although no obvious teratogenic effects have been reported, the possibility of fetal injury cannot be excluded.

The hazards of thiazides crossing the placental barrier include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in adults. Methyldopa and thiazides appear in breast milk. Patients taking ALDORIL should not nurse

Precautions: METHYLDOPA—Should be used with caution in patients w
previous liver disease or dysfunction (see **Warnings**). May interfere with me
urinary uric acid by the phosphotungstate method, serum creatinine by the alka
method, and SGOT by colorimetric methods. Since methyldopa causes fluore
urine samples at the same wavelengths as catecholamines, falsely high levels
catecholamines may be reported. This will interfere with the diagnosis
chromocytoma. It is important to recognize this phenomenon before a patie
possible pheochromocytoma is subjected to surgery. Methyldopa is not recomm
patients with pheochromocytoma. Urine exposed to air after voiding may darker
of breakdown of methyldopa or its metabolites. Involuntary choreoathetotic m
have been observed in patients with severe bilateral cerebrovascular disease
movements occur, stop the drug. Patients may require reduced doses of ane
hypotension occurring during anesthesia usually can be controlled with vasop
Hypertension has recurred after dialysis in patients on methyldopa because the
removed by this procedure.

HYDROCHLOROTHIAZIDE—Perform periodic determination of serum electroly
detect possible electrolyte imbalance. Observe all patients for clinical signs of flu
electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokal
Serum and urine electrolyte determinations are particularly important when patie
vomiting excessively or receiving parenteral fluids. Medication such as digitalis may
influence serum electrolytes. Warning signs, irrespective of cause, are dryness of m
thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, mus
fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances suc
nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, in se
cirrhosis, with concomitant corticosteroids or ACTH, or with inadequate oral electr
intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effect
digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treate
use of potassium supplements, such as foods with a high potassium content. Any chlo
deficit is generally mild and usually does not require specific treatment except unc
extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremi
may occur in edematous patients in hot weather; appropriate therapy is water restriction
rather than administration of salt except in rare instances when the hyponatremia is lif
threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin
requirements in diabetic patients may be increased, decreased, or unchanged; latent
diabetes mellitus may become manifest. Thiazides may increase responsiveness to
tubocurarine. Antihypertensive effects of the drug may be enhanced in postsympathec-
tomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is
not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If
progressive renal impairment becomes evident, consider withholding or discontinuing
diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid
disturbance. Calcium excretion is decreased by thiazides. Pathological changes in the
parathyroid glands with hypercalcemia and hypophosphatemia have been observed in a
few patients on prolonged therapy; thiazides should be discontinued before testing for
parathyroid function.

Adverse Reactions: METHYLDOPA—*Central nervous system:* Sedation, headache, asthenia or weakness; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression. *Cardiovascular:* Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.) *Gastrointestinal:* Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis. *Hepatic:* Abnormal liver function tests, jaundice, liver disorders. *Hematologic:* Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells and rheumatoid factor. *Allergic:* Drug-related fever, lupus-like syndrome, myocarditis. *Other:* Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

HYDROCHLOROTHIAZIDE—*Gastrointestinal system:* Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis. *Central nervous system:* Dizziness, vertigo, paresthesias, headache, xanthopsia. *Hematologic:* Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, hemolytic anemia. *Cardiovascular:* Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics). *Hypersensitivity:* Purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), fever, respiratory distress including pneumonitis, anaphylactic reactions. *Other:* Hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, transient blurred vision. Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

Note: Tolerance may occur, usually between the second and third month of therapy. Increasing dosage of either component separately or together frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

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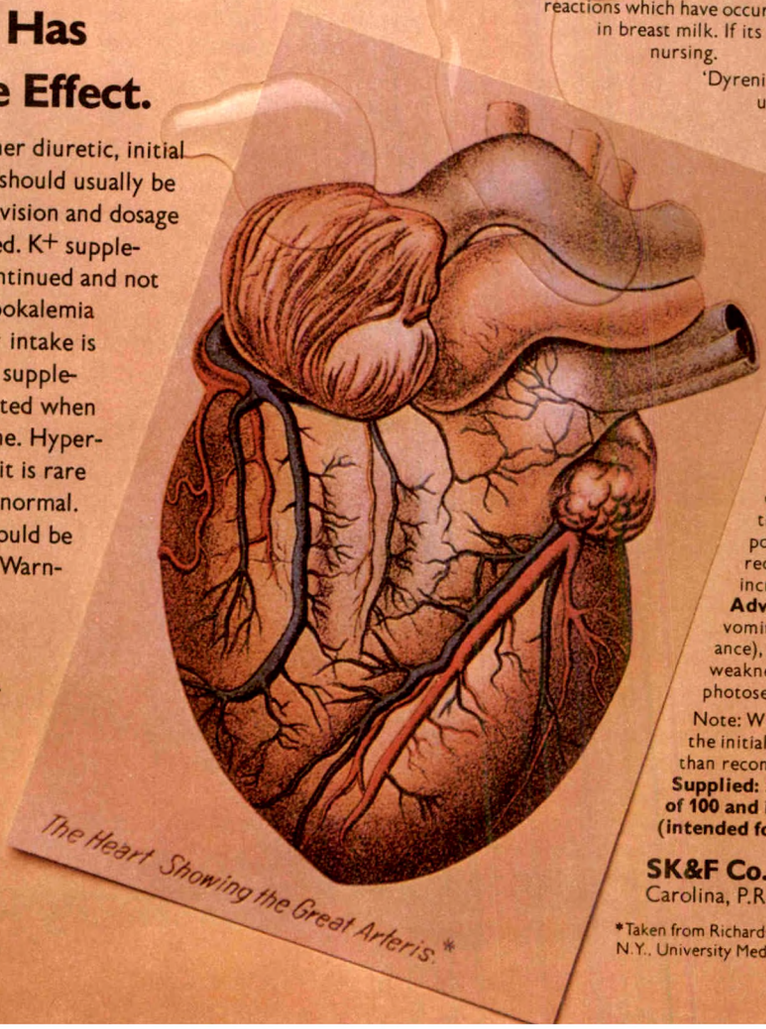
1. Donaldson, E.K., et al.: *Brit. M.J.* 1:1254-5 (May 22) 1976.



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Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Contraindications: Anuria. Severe or progressive kidney disease or dysfunction. Severe hepatic disease. Pre-existing elevated serum potassium. Hypersensitivity. Continued use in developing hyperkalemia. Do not give potassium supplements, either by drug or by diet.

Warnings: Observe regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Check BUN and serum potassium periodically, especially in the elderly, diabetics, and those with suspected or confirmed renal insufficiency. Use in pregnancy requires weighing anticipated benefits against possible hazards to the fetus, including adverse reactions which have occurred in the adult. Triamterene may appear in breast milk. If its use is essential, the patient should stop nursing.

'Dyrenium' and spironolactone are not usually used concurrently; if they are, however, frequent serum potassium determinations are required.

Precautions: If hyperkalemia develops, withdraw the drug. The following may also occur: electrolyte imbalance, low-salt syndrome (with low salt intake), reversible mild nitrogen retention, decreasing alkali reserve with possible metabolic acidosis. Triamterene is a weak folic acid antagonist. Do periodic hematologic studies in cirrhotics with splenomegaly. Concomitant use with antihypertensive drugs may result in an additive hypotensive effect. When 'Dyrenium' is to be discontinued after intensive or prolonged therapy, withdraw gradually because of possible rebound kaliuresis. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Diarrhea, nausea and vomiting (may indicate electrolyte imbalance), other gastrointestinal disturbances, weakness, headache, dry mouth, anaphylaxis, photosensitivity, elevated uric acid, rash.

Note: When combined with another diuretic, the initial dosage of each agent should be lower than recommended.

Supplied: 50 and 100 mg. capsules, in bottles of 100 and in Single Unit Packages of 100 (intended for institutional use only).

SK&F Co.
Carolina, P.R.

*Taken from Richardson, J.G.: Medicology. N.Y., University Medical Society, 1906.

SK&F CO.
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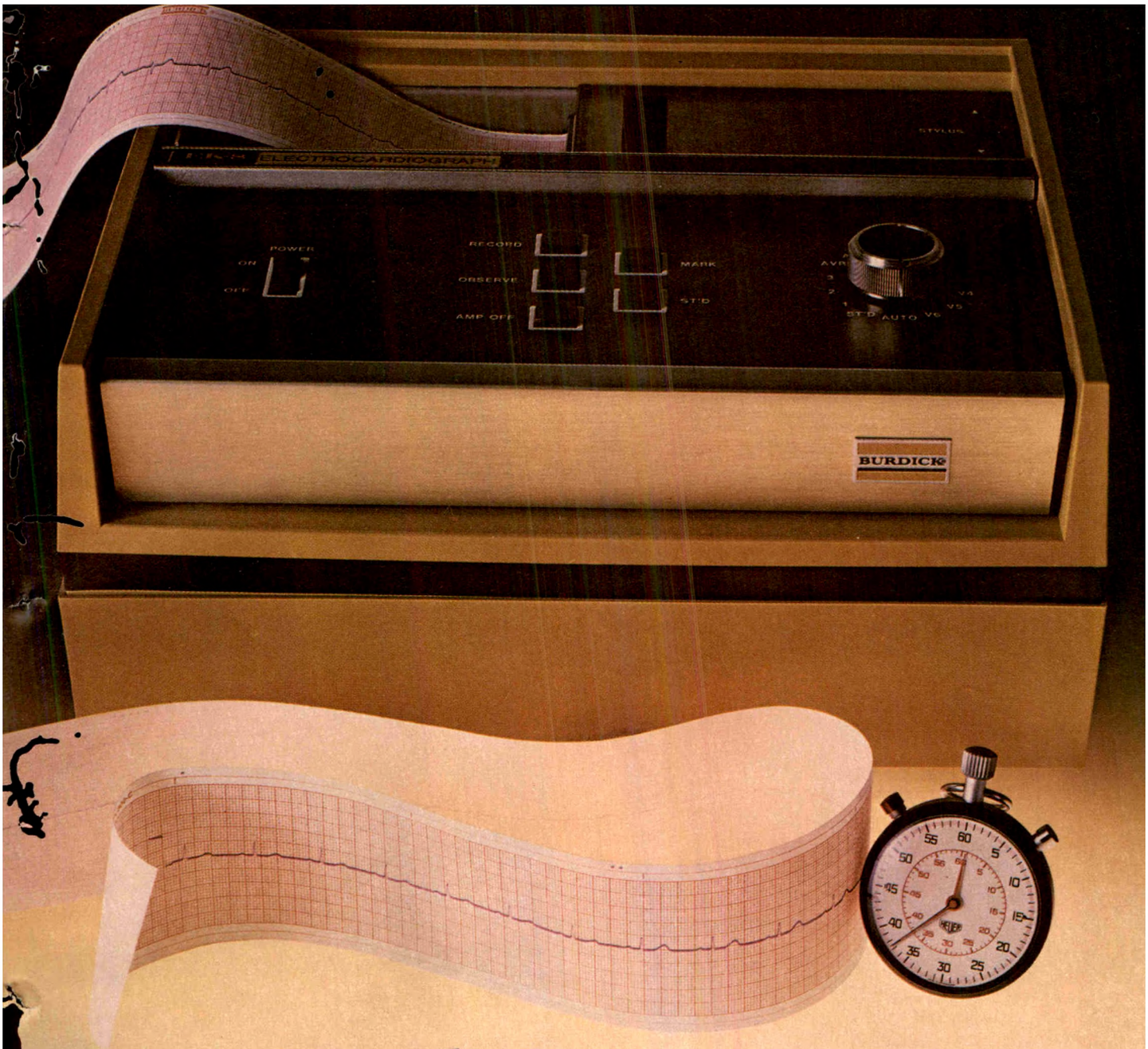

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- **can be mixed with water or other liquid for pleasant daily dosage**
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Please see brief summary of prescribing information on adjoining page.

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26790

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Klorvess® Effervescent Granules and Klorvess® (potassium chloride) 10% Liquid

Brief summary of prescribing information

DESCRIPTION: *Klorvess Effervescent Granules:* Each packet (2.8 g) contains 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, L-lysine monohydrochloride 0.913 g in a sodium-, sugar- and carbohydrate-free effervescent formulation. Dissolution of the packet contents in water provides the potassium and chloride available for oral ingestion as potassium chloride, potassium bicarbonate, potassium citrate and L-lysine monohydrochloride.

Klorvess (potassium chloride) 10% Liquid: Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

INDICATIONS: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

CONTRAINDICATIONS: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

PRECAUTIONS: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements. Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis. High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest. To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve the packet contents of *Klorvess Effervescent Granules* in 3 to 4 ounces of cold water, fruit juice or other liquid or dilute each tablespoonful of *Klorvess (potassium chloride) 10% Liquid* in 3 to 4 ounces of cold water. Both of these solutions should be ingested slowly with or immediately after meals.

ADVERSE REACTIONS: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts. The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest. The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

DOSAGE AND ADMINISTRATION: *Klorvess Effervescent Granules:* Adults—One packet completely dissolved 2 to 4 times daily depending upon the requirements of the patient.

Klorvess (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) completely diluted in cold water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating.

OVERDOSAGE: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

HOW SUPPLIED: *Klorvess Effervescent Granules*—packages of 30 packets (2.8 g each). *Klorvess (potassium chloride) 10% Liquid* (dark red)—as a cherry-with-pit flavored liquid in pint and gallon bottles. Klorvess Effervescent Granules and Liquid are also available in institutional packaging as follows: *Klorvess Effervescent Granules*—packages of 1000 packets; *Klorvess Liquid*—36 (3 x 12) x 4 oz Unit-of-Use bottles and 100 (4 x 25) x 15 ml Unit-Dose bottles.

(For complete details, please consult full prescribing information)

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SUMMARY OF PRESCRIBING INFORMATION

* **Indications:** Based on a review of this drug by The National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"**Probably**" **effective:** The sublingual dosage form of SORBITRATE is indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety.

Precautions: Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an angina attack. SORBITRATE® Sublingual (isosorbide dinitrate) may be taken for prompt relief of angina pain three or four times daily. Although the onset and duration of effect of coronary nitrates may vary, following is the generally reported range of these values for SORBITRATE® Sublingual.

Onset of Effect: Two to five minutes.
Duration of Effect: One to two hours.

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OCTOBER 1, 1979

The American Journal of CARDIOLOGY®

VOLUME 44

NUMBER 4

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CLINICAL STUDIES

585 **Serial Noninvasive Assessment of Left Ventricular Hypertrophy and Function After Surgical Correction of Aortic Regurgitation**

GERHARD SCHULER, KIRK L. PETERSON, ALLEN D. JOHNSON, GARY FRANCIS, WILLIAM ASHBURN, GEORGE DENNISH, PAT O. DAILY and JOHN ROSS, Jr.

Data obtained from serial M mode echocardiographic analyses of left ventricular hypertrophy and function, validated by first pass radionuclide angiography in 16 patients before and after surgical correction of severe aortic valve regurgitation, demonstrate that aortic valve replacement for symptomatic aortic regurgitation prior to severe myocardial decompensation improves clinical status, causes regression of myocardial hypertrophy, reduces left ventricular size, improves normal mass/volume ratio and lessens septal dyskinesia. Provided septal dyskinesia was not present, echocardiographic and first pass radionuclide determinations of ejection fraction correlated highly.

595 **Abbreviation of Systolic Time Intervals in Acute Mitral Regurgitation: Effect of Prosthetic Mitral Valve Replacement**

HARISIOS BOUDOULAS, RICHARD P. LEWIS, STEPHANOS DERVENAGAS, MARY ELIZABETH FONTANA and JOHN S. VASKO

Systolic time interval measurements in 26 patients with mitral regurgitation and in 13 of these after mitral valve replacement revealed that the PEP/LVET ratio increased in all patients 2 weeks after operation, but the increase was greater in those with lower preoperative values for this ratio. A decrease in preload remains the most attractive explanation of the early postoperative increase in the PEP/LVET ratio. Serial studies performed over 6 months showed a return toward the preoperative value. These results indicate that systolic time intervals are useful for assessing left ventricular performance in all types of mitral regurgitation, and especially for distinguishing between acute and chronic regurgitation. Evaluation of left ventricular performance after valve replacement for mitral regurgitation is best postponed until at least 6 months after operation.

601 **Effects of Coronary Bypass Grafting on Resting Left Ventricular Contraction in Patients Studied 1 to 2 Years After Operation**

LEONARD M. ZIR, ROBERT DINSMORE, MICHAEL VEXERIDIS, JANG B. SINGH, J. WARREN HARTHORNE and WILLARD M. DAGGETT

Angiographic evaluation of left ventricular contraction 1 or 2 years after successful coronary arterial bypass surgery in 51 patients characterized by a low preoperative infarction rate and a higher graft patency rate revealed a significant reduction in left ventricular segmental wall motion abnormalities and only a small incidence of deterioration in contraction. In these 51 patients a total of 95 vein grafts and 4 left internal mammary to left anterior descending arterial grafts were performed (approximately 2 grafts per patient); the late graft patency rate was 95 percent. Three had a perioperative myocardial infarction; one had an infarction in the year after operation; and there were no late deaths in the study population. The investigators believe it unlikely that the postoperative lessening of asynergy reflects the absence of propranolol, which most patients took before their preoperative catheterization and few during their postoperative catheterization.

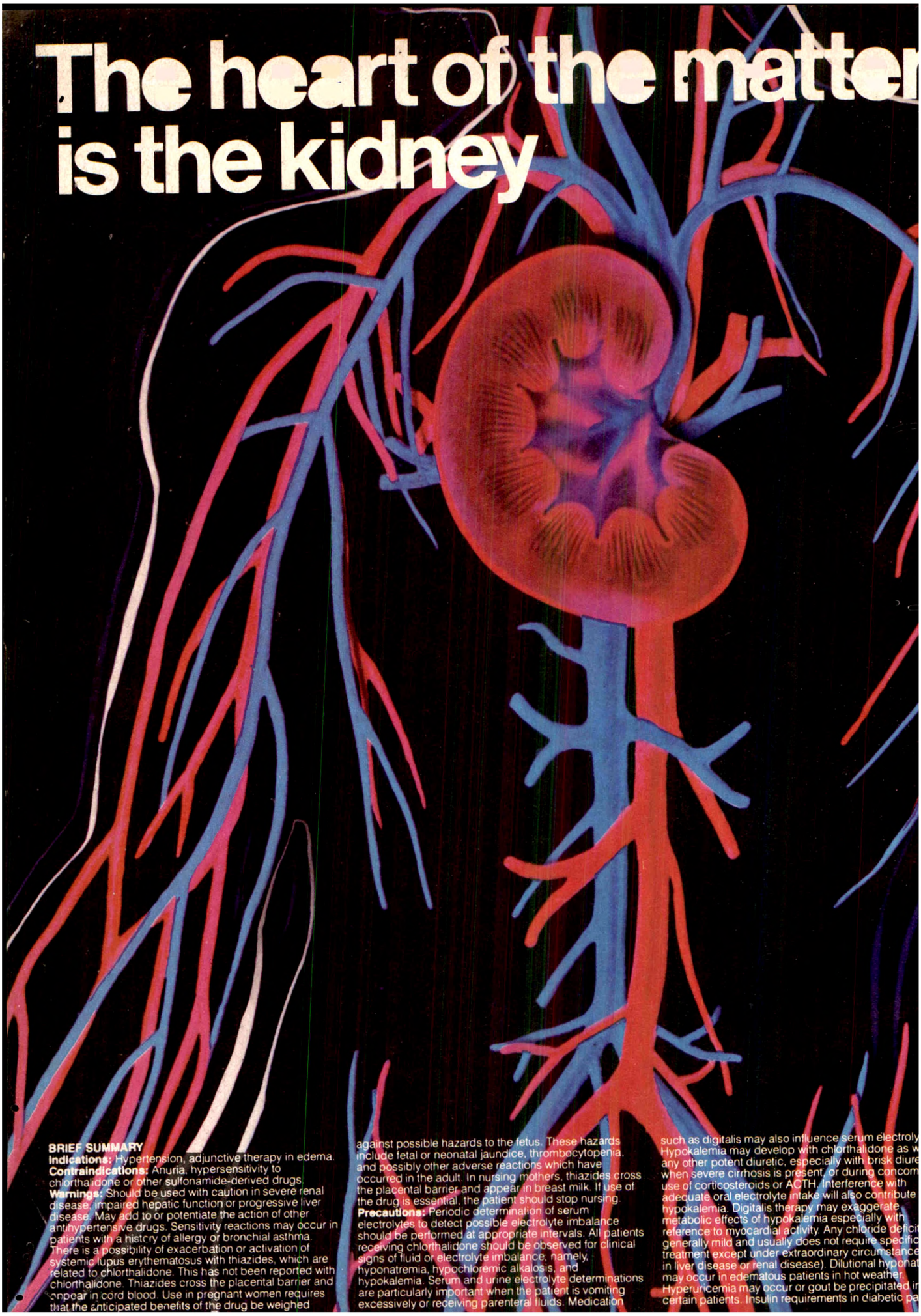
607 **Reversal of Exertional Hypotension After Coronary Bypass Grafting**

WEI-I LI, ROBERT C. K. RIGGINS and RICHARD P. ANDERSON

In a subgroup of 37 patients with symptomatic angina pectoris and exertional hypotension before operation, coronary bypass surgery improved hemodynamic and electrocardiographic status and reversed exertional hypoten-

Continued on page A15

The heart of the matter is the kidney



BRIEF SUMMARY
Indications: Hypertension, adjunctive therapy in edema.
Contraindications: Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs.
Warnings: Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. There is a possibility of exacerbation or activation of systemic lupus erythematosus with thiazides, which are related to chlorthalidone. This has not been reported with chlorthalidone. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing.
Precautions: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electroly Hypokalemia may develop with chlorthalidone as w any other potent diuretic, especially with brisk diure when severe cirrhosis is present, or during concom use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride defici generally mild and usually does not require specific treatment except under extraordinary circumstance in liver disease or renal disease). Dilutional hyponat may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic pa

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(chlorthalidone USP)
Gets to the heart of the matter...simply

may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance. **Adverse Reactions:** Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn. **Usual Dose:** One tablet daily. **How Supplied:** Tablets—100 mg. (white, scored), 50 mg. (aqua) and 25 mg. (peach) in bottles of 100 and 1000; unit-dose blister packs, boxes of 100 (10 x 10 strips). Also, 100 mg. and 50 mg. in PAKs of 28 tablets, boxes of 6.

References: 1. Finnerty, F.A. Jr.: Managing Mild Hypertension: A low-dose approach, Scientific Exhibit presented at Amer. Coll. Cardiol. 28th Annual Scientific Session, Miami Beach, Fla., Mar. 11-15, 1979. **2.** Materson, B.J. et al.: Dose response to chlorthalidone in patients with mild hypertension, Clin. Pharmacol. Ther. 24:192, 1978. **3.** Data on file, USV Laboratories Inc.

USV LABORATORIES

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Manati, P.R. 0070[illegible]

*INDICATIONS—Based on a review of this drug by the National Academy of Science-National Research Council and/or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.

ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg (2 tablets) three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy. Tablets of 25 mg

For complete details, please see the full prescribing information.

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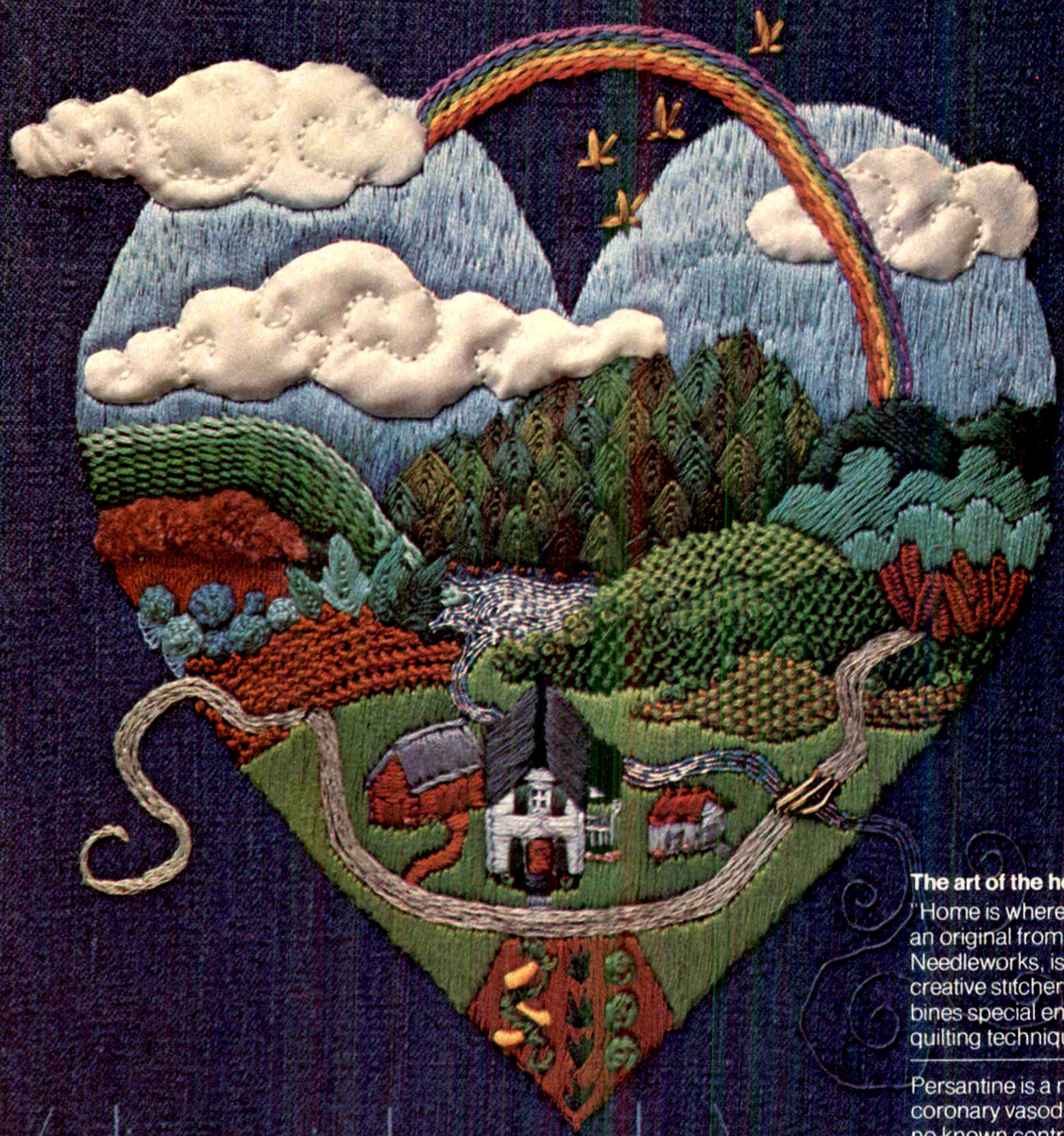

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(dipyridamole)

Persantine

sion in 33 and produced normal exercise electrocardiograms in 29. These studies show that the decrease in systolic blood pressure that occurs with treadmill exercise testing may be a sign of reversible ischemic left ventricular dysfunction. Reversal of exertional hypotension appears to be a desirable result of coronary bypass surgery and a good index of alleviation of exertional myocardial ischemia, but the effect of such surgery on longevity remains unknown.

612 **Improved Survival Beyond 5 Years After Coronary Bypass Surgery in Patients With Left Main Coronary Artery Disease**

GERALD M. LAWRIE, GEORGE C. MORRIS, Jr., JIMMY F. HOWELL, MARC HINES and DON W. CHAPMAN

This study of 134 consecutive patients with greater than 50 percent stenosis of the luminal diameter of the main left coronary artery subjected to bypass surgery between 1968 and 1973 revealed a survival rate of 79 percent for the total group, 81 percent in patients with good ventricular function and 76 percent in those with poor ventricular function. Comparison with the normal U.S. population of identical age and sex indicates that late attrition is almost normal after operation in patients with good ventricular function, and excellent long-term survival can be expected from operation in these patients with severe disease and good preoperative left ventricular function. A major advance in surgical technique—the introduction of myocardial preservation with use of cold potassium cardioplegia and topical cardiac hypothermia—has notably improved the perioperative course of these patients by reducing the incidence of low output syndrome and arrhythmias.

616 **Correlation of Thallium-201 Scintigrams With Coronary Anatomy: Factors Affecting Region by Region Sensitivity**

BARRY M. MASSIE, ELIAS H. BOTVINICK and BRUCE H. BRUNDAGE

Evaluating the effect of the severity and distribution of coronary arterial involvement and of the presence of areas of previous myocardial infarction in 78 of 100 consective patients who had both coronary arteriography and myocardial perfusion scintigraphy within 14 days, these studies show that the sensitivity of exercise thallium-201 scintigraphy is not impaired by the presence of widespread coronary disease or areas of old infarction. The severity of the corresponding stenosis is the most important factor determining the regional sensitivity of scintigraphy and the number of involved vessels is the major factor affecting sensitivity in an individual patient. Thallium-201 myocardial perfusion scintigraphy is highly specific for coronary artery disease and quite sensitive, even in patients without previous infarction. However, in most patients some jeopardized regions will not be detected, particularly lesions of the left circumflex coronary artery and those that are less severe. As a result, one drawback of this technique is that it does not permit precise quantitation of the number of vessels involved and is less reliable in estimating the anatomic extent of coronary disease than in diagnosing its presence.

623 **Mechanism of Ventricular Fibrillation. Observations Based on Electrode Catheter Recordings**

MARK E. JOSEPHSON, SCOTT R. SPIELMAN, ALLAN M. GREENSPAN and LEONARD N. HOROWITZ

These observations in 16 patients on the initiation (spontaneous or induced) and spontaneous termination of ventricular fibrillation in human beings using endocardial electrode catheter recordings are compatible with the multiple wavelet (reentrant) theory of ventricular fibrillation. In 11 patients ventricular fibrillation was initiated by programmed ventricular stimulation and in 5 patients ventricular fibrillation occurred spontaneously. At least two stimulated ventricular premature depolarizations of increasing prematurity, usually followed by further acceleration of local ventricular electrograms, were required to provide the substrate for degeneration into ventricular fibrillation. A second mode of initiation of ventricular fibrillation resulted from ventricular tachycardia that underwent sudden acceleration and degeneration to a disorganized rhythm.

632 **R on T or R on P Phenomenon? Relation to the Genesis of Ventricular Tachycardia**

KUANG-HUNG TYE, ANIL SAMANT, KENNETH B. DESSER and ALBERTO BENCHIMOL

Continuous electrocardiographic monitoring of 225 patients with acute myocardial infarction during the first 48 hours after admission to a hospital revealed 212 episodes of ventricular tachycardia in 49 subjects and primary ventricular fibrillation in 8. A premature complex on the T wave (R on T) initiated the ventricular tachycardia in 20 percent and directly after the onset of the sinus P wave (R on P) in 44 percent. Seven of the eight episodes

Continued on page A19

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Wax-matrix tablets minimize likelihood of GI complications. The special wax matrix used in KAON-CL TABS permits gradual release of potassium chloride in the GI tract. Because the potassium is slowly released, the possibility of high localized GI concentrations is limited. The reported frequency of GI lesions with wax-matrix tablets is less than one per 100,000 patient-years. There have been only two equivocal cases of GI bleeding reported with KAON-CL TABS to date and no reports of small bowel stenosis or ulceration. However, clinical experience is insufficient at this time to indicate that the incidence is other than the stated numerical ratio.

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(potassium chloride) Controlled Release Tablets

For summary of prescribing information, please see following page.

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BRIEF SUMMARY

KAON-Cl TABS® (potassium chloride) Controlled Release Tablets

Description: Kaon-Cl Tabs is a sugar coated (not enteric-coated) tablet containing 500 mg potassium chloride (equivalent to 6.7 mEq potassium chloride) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

Indications: BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUIDS OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure, hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

Contraindications: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium. Potassium supplementation, when indicated in such patients, should be with a liquid preparation.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

Warnings: *Hyperkalemia*—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Kaon-Cl Tabs (potassium chloride) is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient years. Kaon-Cl Tabs should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Adverse Reactions: The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

The most severe adverse effects are hyperkalemia (see Contraindications, Warnings and Overdosage) and gastrointestinal obstruction, bleeding or perforation (see Warnings).

Overdosage: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see Contraindications and Warnings). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-wave, depression of S-T segment, and prolongation of the QT interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and potassium-sparing diuretics.
2. Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10-20 units of crystalline insulin per 1,000 ml.
3. Correction of acidosis, if present, with intravenous sodium bicarbonate.
4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

Caution: Federal law prohibits dispensing without prescription.

How Supplied: Bottles of 100, 250 and 1000.

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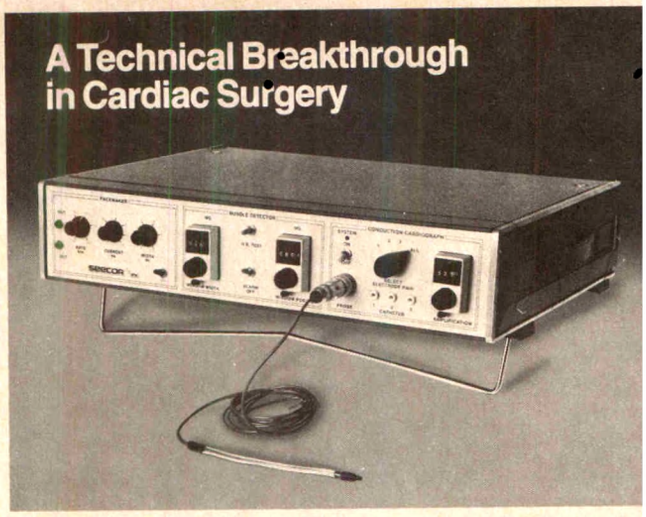

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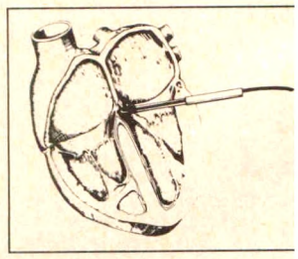

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References:

Siegel, L., Mahoney, E. B., Manning, J. A., and Stewart, S.: **An Audible Alarm System to Facilitate the Intraoperative Identification of Cardiac Conduction Tissue,** *The Journal of Thoracic and Cardiovascular Surgery,* 68:241, August, 1974.

Green, R., Siegel, L., Hill, A., DeWeese, J. A., and Stewart, S.: **Regional Myocardial Infarction at Operation — An Automated System of Identification,** *Archives of Surgery,* 110:1416, November, 1975.

See the CARDIO-PROBE at the Annual Meeting of American College of Chest Physicians, Booth 217 American Heart Association, Booth F-104

of ventricular fibrillation were initiated by a premature ventricular complex and in four there was an associated R on T phenomenon. It is suggested that the influence of atrial contraction and myocardial stretch on reentry or ectopy may possibly explain the relatively large incidence of ventricular tachycardia after the onset of the sinus P wave.

638 **Epicardial Activation in Human Left Anterior Fascicular Block**

CHRISTOPHER R. WYNDHAM, MOOIDEEN K. MEERAN, THOMAS SMITH, RICHARD M. ENGELMAN, SIDNEY LEVITSKY and KENNETH M. ROSEN

Epicardial mapping studies during coronary arterial bypass surgery indicate that the marked left axis deviation in four patients with coronary artery disease reflects delayed activation of the basal anterolateral left ventricle and is consistent with the presence of block or delay in the anterior "fascicle" of the left bundle branch. These results tend to confirm the concept of electrocardiographic left anterior fascicular block in which this pattern correlates with the presence of focal delay in activation of the basal anterolateral left ventricular wall.

645 **Left Anterior Fascicular Block: Electrocardiographic Criteria for Its Recognition in the Presence of Inferior Myocardial Infarction**

MICHAEL L. FISHER, MARC A. MUGMON, NATHAN H. CARLINER, CHARLES E. DeFELICE and GARY D. PLOTNICK

With current established criteria for left anterior fascicular block (hemiblock) (leftward deviation of the mean [frontal] QRS axis and the concomitant presence of normal initial forces, including initial positive deflections [r waves] in the inferior leads [II, III and aVF]), this condition cannot be reliably diagnosed in patients with inferior myocardial infarction manifested by Q waves in leads II, III and aVF. Using vectorcardiographic criteria that permit the recognition of a conduction delay in the left anterior fascile with or without an associated inferior myocardial infarction, these investigators propose that, in the absence of bundle branch block, a mean QRS axis between 0° and −90°, a deep negative terminal deflection in lead II and a positive terminal deflection in lead aVR should indicate left anterior fascicular block with or without an associated inferior myocardial infarction. Of the 47 patients who met the strict vectorcardiographic criteria for left anterior fascicular block 94 percent showed the predicted electrocardiographic pattern, including 24 of 26 (92 percent) who had both this conduction defect and inferior wall myocardial infarction.

EXPERIMENTAL STUDIES

651 **Experimental Studies on the Pathogenesis of Asystole After Verapamil in the Dog**

FERDINAND URTHALER and THOMAS N. JAMES

In these dog studies concentrations of verapamil that do not produce high grade heart block in the normal heart readily caused high grade block and prolonged ventricular standstill after elimination of adrenergic influences in the atrioventricular (A-V) junction. Verapamil selectively perfused into the A-V nodal artery caused transient complete A-V block. Only AVJ-2 rhythm, sometimes alternating with a slow AVJ-1 rhythm, emerged. The investigators postulate that verapamil impairs A-V conduction through depression of cells in the upper segment of the A-V junction and that complete A-V block occurs when most, but not all, of the A-V junction is markedly depressed. If human cardiac responses are similar to those in dogs, then due caution should accompany the use of verapamil in patients receiving beta receptor blocking agents and in those with congestive heart failure whose myocardial stores are diminished.

657 **Comparative Effects of Cardioselective Versus Noncardioselective Beta Blockade on Subendocardial Blood Flow and Contractile Function in Ischemic Myocardium**

JAMES D. BUCK, GARRETT J. GROSS, DAVID C. WARLTIER, STANLEY R. JOLLY and HAROLD F. HARDMAN

This investigation compares the distribution of blood flow and contractile function in the ischemic myocardium of anesthesized dogs after the use of practolol (a cardioselective beta adrenergic antagonist with intrinsic sympathomimetic properties), bevantolol (a cardioselective agent that lacks intrinsic activity) and propranolol (a nonselective beta antagonist). All three compounds significantly decreased heart rate and tension-time index. Pro-

Continued on page A23

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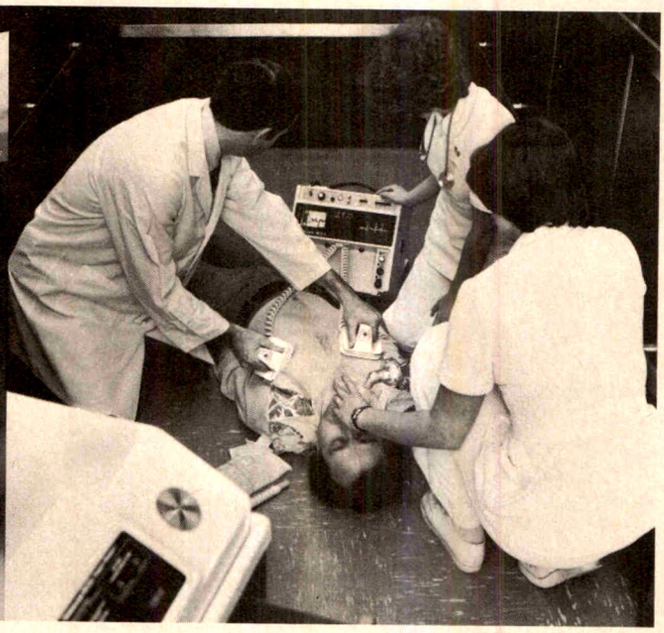

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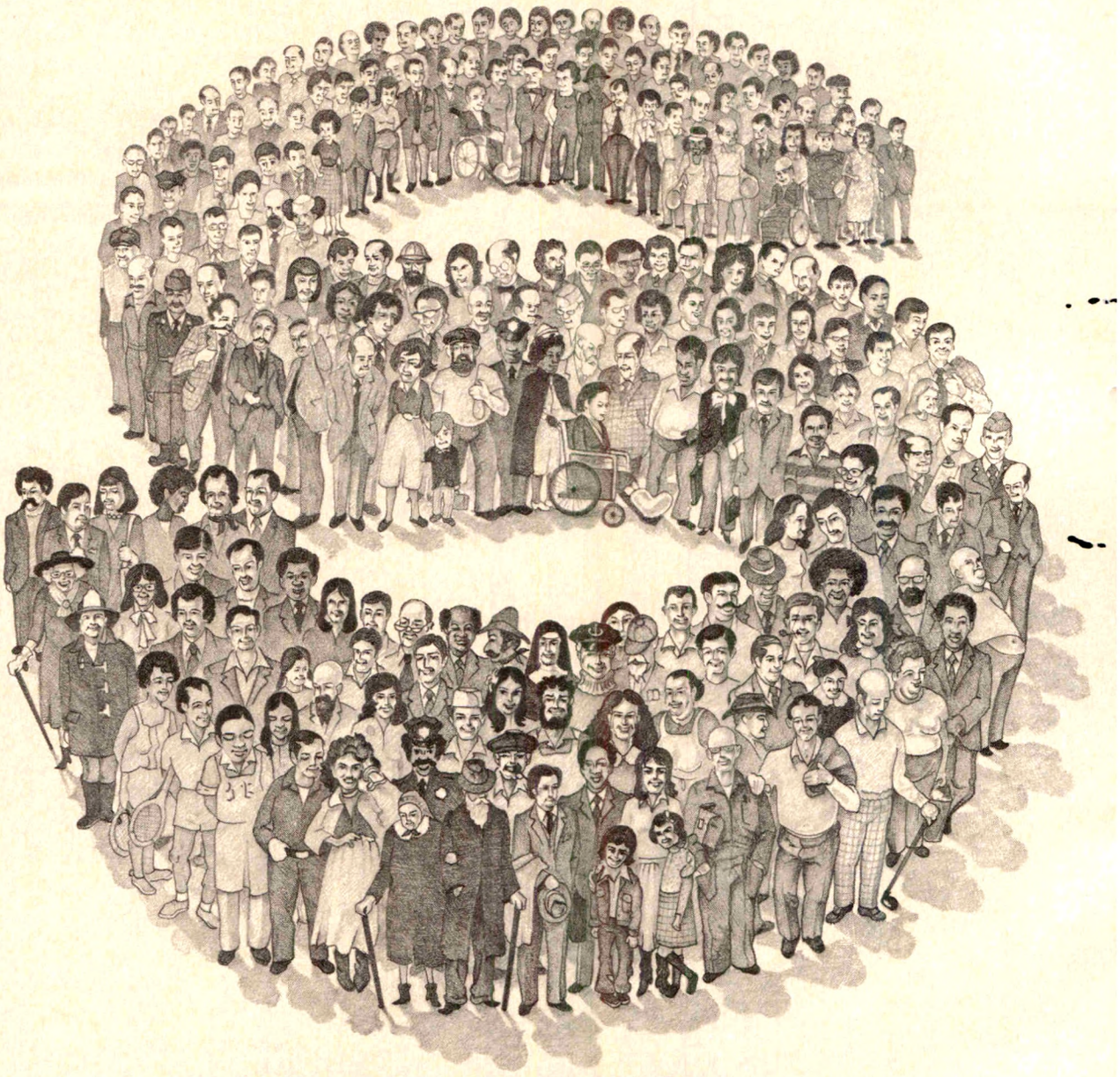

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pranolol (−33 percent) and bevantolol (−11 percent) significantly decreased the contractile force in the normal area; practolol produced no change. After bevantolol, subendocardial flow, contractile function and endocardial/epicardial ratio significantly increased, indicating a possible advantage of this agent over the others. These results suggest that blood flow is redistributed within an ischemic area of the myocardium after either $beta_1$ or simultaneous $beta_1$ and $beta_2$ receptor blockade.

664 **Quantification of Thallium-201 Scintigrams in Acute Myocardial Infarction**

A. DENNIS NELSON, SUBHASH KHULLAR, RICHARD F. LEIGHTON, G. COLIN BUDD, AMIRA GOHARA, JAMES N. ROSS, Jr., LEE T. ANDREWS and JOSEPH WINDHAM

This study in 16 dogs after ligation of the left anterior descending artery, using computer-processed thallium-201 scintigrams indicates that scintigraphic quantitation of infarct size is feasible in the dog model when the infarct volumes are less than 15 percent of left ventricular myocardium. The best projection for quantitation of infarct size will be one in which there is least overlap between normal and damaged myocardium. The use of this technique in the clinical setting will require further corroboration by clinical and autopsy data.

METHODS

670 **Two Dimensional Echocardiographic Evaluation of Patients With Mitral Insufficiency**

GARY S. MINTZ, MORRIS N. KOTLER, BERNARD L. SEGAL and WAYNE R. PARRY

Two dimensional echocardiography in 140 patients with clinical mitral insufficiency revealed that mitral valve prolapse was the most common cause (41 patients), followed by rheumatic heart disease with combined mitral stenosis and insufficiency (27) or pure mitral insufficiency (10), mitral anular calcification (11), idiopathic hypertrophic subaortic stenosis (5), left anterior mitral leaflet (5) and atrial myxoma (1). This technique reliably differentiated mitral insufficiency secondary to valve disease from that secondary to ventricular or papillary muscle dysfunction.

679 **Serum Myocardial Creatine Kinase (CK-MB) After Coronary Arterial Bypass Surgery**

HANS R. BAUR, BERNARD W. STEELE, KENNETH F. PREIMESBERGER and FREDARICK L. GOBEL

Serum myocardial creatine kinase (CK-MB) determination by column chromatography is shown to be a reliable test for the recognition of perioperative myocardial infarction. Studies in 100 consecutive patients after coronary arterial bypass surgery also indicate it is more sensitive than electrocardiography or scintigraphy for detection of myocardial necrosis in the early postoperative period. The association of an elevated serum CK-MB level with additional other positive tests strengthens its reliability. Peak CK-MB levels occurred at an average interval of 9.2 ± 5.8 (standard deviation) hours after operation in patients with perioperative myocardial infarction compared with only 4.7 ± 3.3 hours in patients without this complication, suggesting direct surgical trauma produces immediate short term liberation of the enzyme into the circulation whereas perioperative necrosis with reperfusion results in more prolonged and slower release of CK-MB. A single determination 6 to 12 hours after operation may be sufficient to indicate the possibility of postoperative complications in patients with high enzyme values and certainly is easier to obtain and less expensive than myocardial scintigraphy.

PEDIATRIC CARDIOLOGY

687 **Critical Aortic Coarctation: Patch Aortoplasty in Infants Less Than Age 3 Months**

WILLIAM H. FLEMING, LYNNE B. SARAFIAN, EDWARD B. CLARK, KENNETH J. DOOLEY, PHILIP J. HOFSCHIRE, ALAN R. HOPEMAN, ROGER N. RUCKMAN and PAUL K. MOORING

These favorable results after patch aortoplasty in 23 infants less than 3 months old indicate that surgical repair of critical coarctation of the aorta in infants can safely be offered despite the presence of other cardiac anomalies. All survived surgical repair and had clinical alleviation of congestive heart failure. Pulmonary arterial banding should be deferred until after repair of the coarctation to allow intracardiac hemodynamics to equilibrate before banding.

Continued on page A27

024 118

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1. *HEW News*, publication 79-6. U.S. Department o Health, Education, and Welfare (Food and Drug Administration), March 30, 1979, p. 1.

†Data on file and available upon request from Hoechst-Roussel Pharmaceuticals Inc., Somerville, N.J. 08876.

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INDICATIONS: Edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Hypertension when used alone or in combination with other antihypertensive drugs; patients not adequately controlled with thiazides also probably will not be adequately controlled with furosemide alone.

CONTRAINDICATIONS: Because animal reproductive studies have shown that furosemide may cause fetal abnormalities, the drug is contraindicated in women of childbearing potential. Anuria. History of hypersensitivity to the compound.

WARNINGS: Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Exercise care in patients receiving potassium-depleting steroids. Perform frequent serum electrolyte, CO_2, and BUN determinations during first few months of therapy and periodically thereafter, and correct abnormalities or temporarily withdraw the drug. Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital. Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Discontinue furosemide if increasing azotemia and oliguria occur during treatment of severe, progressive renal disease. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions. Furosemide may potentiate the therapeutic effect of other antihypertensive agents. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Exacerbation or activation of systemic lupus erythematosus may occur. Furosemide appears in breast milk. If use of the drug is essential, the patient should stop nursing. Cases of tinnitus and reversible hearing impairment have been reported.

There have also been some reports of cases in which irreversible hearing impairment occurred. Usually ototoxicity has been reported when furosemide was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were given. If the physician elects to use high-dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, an infusion rate not exceeding 4 mg furosemide per minute has been used.)

PRECAUTIONS: As with any effective diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Patients receiving furosemide should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with furosemide as with any other potent diuretic, especially with brisk diuresis, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis may exaggerate metabolic effects of hypokalemia, especially with reference to myocardial activity. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Periodic serum calcium levels should be obtained. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Furosemide has a tendency to antagonize the effects of tubocurarine and may potentiate the action of succinylcholine. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Furosemide may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

It has been reported in the literature that coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of Lasix (furosemide) in some patients. This effect has been attributed to inhibition of prostaglandin synthesis by indomethacin. Indomethacin may also affect plasma renin levels and aldosterone excretion; this should be borne in mind when a renin profile is evaluated in hypertensive patients. Patients receiving both indomethacin and Lasix (furosemide) should be observed closely to determine if the desired diuretic and or antihypertensive effect of Lasix (furosemide) is achieved.

ADVERSE REACTIONS: Anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, blurred vision, tinnitus and hearing loss, anemia, leukopenia, agranulocytosis (rare), thrombocytopenia, aplastic anemia (rare), purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), exfoliative dermatitis, erythema multiforme, pruritus. Orthostatic hypotension may occur and may be exaggerated by alcohol, barbiturates, or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis.

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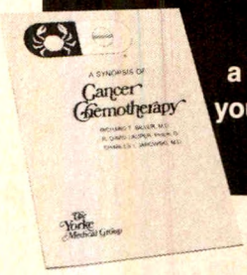
How to Keep Up with Drug Interaction in Cancer Chemotherapy



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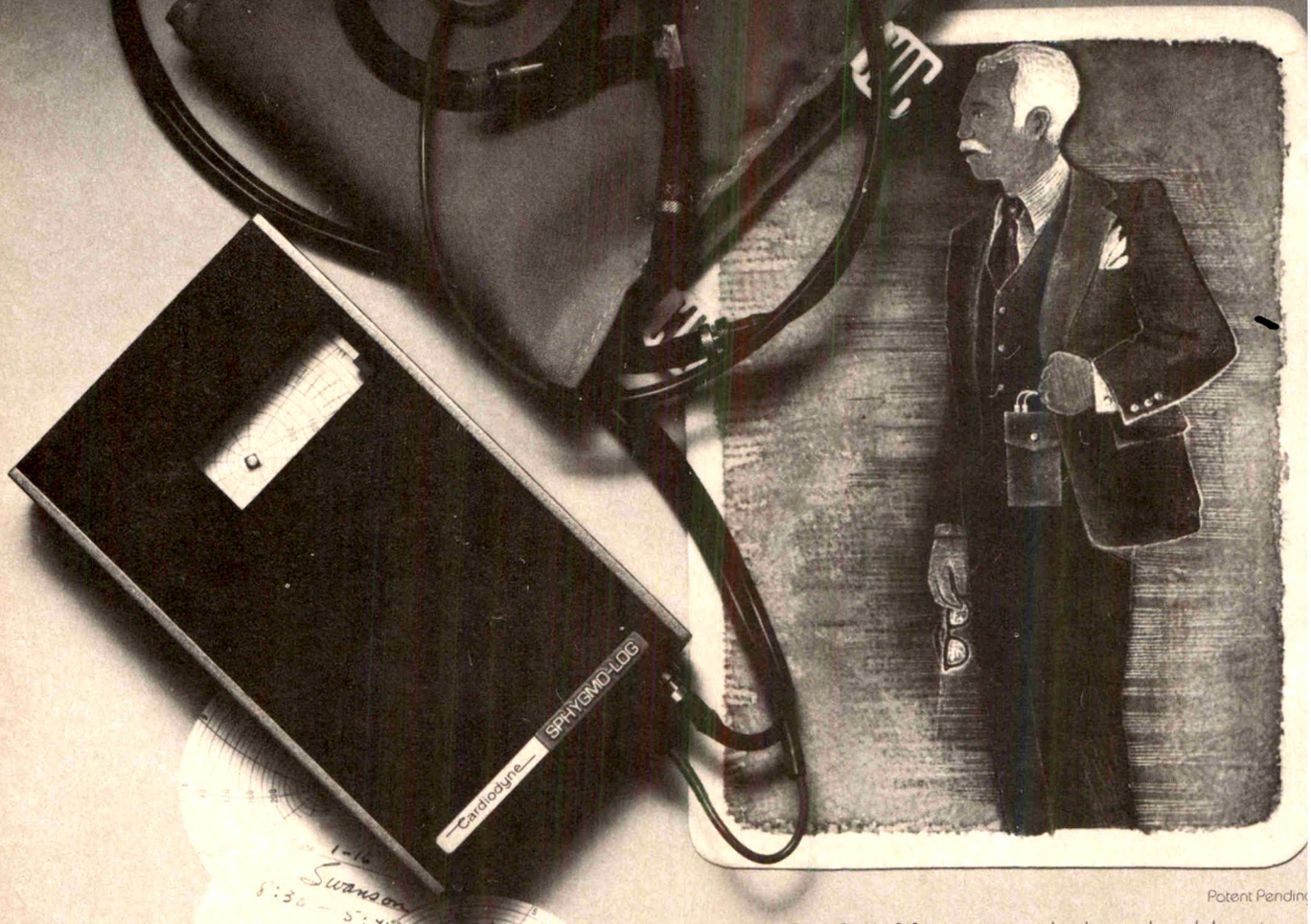

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CONTENTS

691 **Role of Prostaglandin E_1 Infusion in the Management of Transposition of the Great Arteries**

LEE N. BENSON, PETER M. OLLEY, RAMON G. PATEL, FLAVIO COCEANI and RICHARD D. ROWE

Prostaglandin E_1 infusion started in 10 newborn infants with d-transposition of the great arteries and patent ductus arteriosus after balloon atrial septectomy because of a persistently low systemic oxygen saturation of 26 ± 12 percent and oxygen tension of 17 ± 5 torr increased systemic oxygen saturation to 53 ± 19 percent and oxygen tension to 30 ± 9 torr. These data suggest that dilation of the ductus by prostaglandin E_1 infusion increases pulmonary blood flow (left to right shunt), which in turn favorably influences atrial mixing (left to right shunt) and increases systemic oxygen saturation. Pulmonary blood flow may further be increased by a decrease in pulmonary vascular resistence induced by prostaglandin E_1. However, ductal dilatation and increased pulmonary blood flow are not entirely beneficial because they could precipitate congestive heart failure. A palliative Blalock-Hanlon operation (atrial septectomy) or an intraatrial baffle procedure should be arranged on an elective basis, if dependence on prostaglandin E_1 persists.

697 **Blood Pressure, Heart Rate, Pressure-Rate Product and Electrocardiographic Changes in Healthy Children During Treadmill Exercise**

DONALD A. RIOPEL, ASHBY B. TAYLOR and ARNO R. HOHN

This article establishes physiologic data for clinical use and reference values for healthy black and white children during treadmill exercise at a speed of 3.5 miles/hour and a 2 percent elevation of grade at the end of each minute of exercise. The systolic pressure elevation was greatest in the first minute of exercise in all age groups and a more gradual increase in systolic pressure occurred thereafter. The excellent reproducibility of systolic blood pressure responses with repeated exercise tests in this study suggests that blood pressure recordings may be a valuable tool to evaluate such defects as coarctation of the aorta and aortic stenosis.

REPORTS ON THERAPY

705 **Use of Isoproterenol As an Aid to Electric Induction of Chronic Recurrent Ventricular Tachycardia**

C. PRATAP REDDY and LEONARD S. GETTES

Small doses of isoproterenol administered to 11 consecutive patients with symptomatic recurrent ventricular tachycardia in whom standard stimulation techniques failed to induce tachycardia facilitated the induction of such tachycardias. Before isoproterenol, single and double ventricular premature depolarizations and rapid ventricular pacing did not produce the tachycardia; after 6 to 16 μg of isoproterenol was injected intravenously, such pacing could reproducibly initiate and terminate the arrhythmia in six of seven patients with nonsustained ventricular tachycardia and in three of four patients with sustained ventricular tachycardia. Propranolol or procainamide effectively blocked the arrhythmia-facilitating effect of isoproterenol in four and three patients, respectively. In two patients neither agent was effective. The precise mechanism by which isoproterenol facilitated the induction of such tachycardia remains uncertain.

714 **Effects of Oral Quinidine on Left Ventricular Performance in Normal Subjects and Patients With Congestive Cardiomyopathy**

MICHAEL H. CRAWFORD, DAVID H. WHITE and ROBERT A. O'ROURKE

Echocardiographic studies in 10 normal subjects and 8 patients with congestive cardiomyopathy showed that oral quinidine therapy had little adverse effect on left ventricular performance at rest or during acute pressure loading. Results in normal subjects suggest that quinidine may have a mild depressant effect on myocardial function that is masked by the vagolytic effect of the drug. These changes are not seen in patients with compromised myocardial function.

SEMINAR ON MYOCARDIAL OXYGEN UTILIZATION

719 **Introduction: Physiologic and Clinical Correlates**

KARL T. WEBER

Continued on page A31

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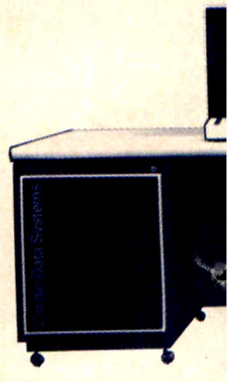

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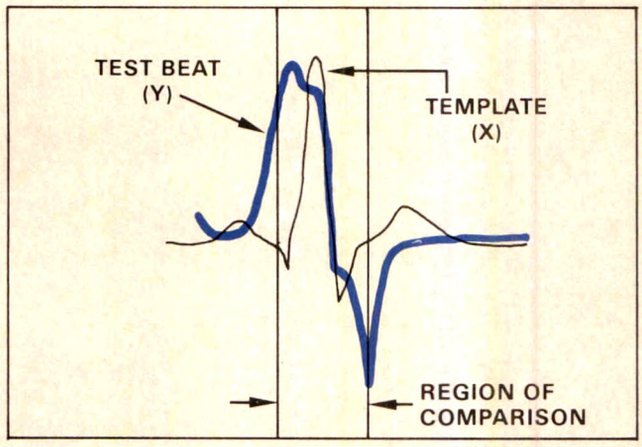

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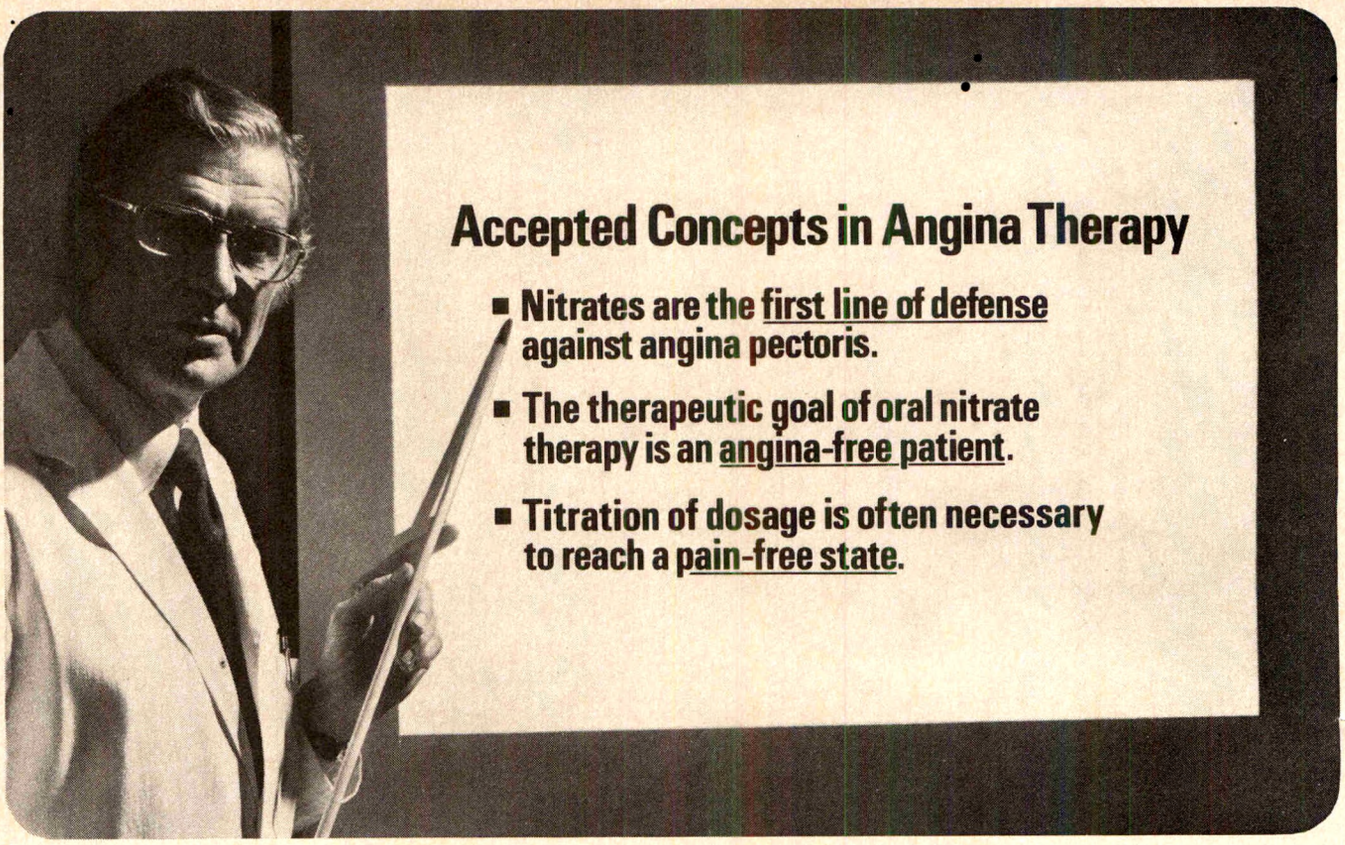

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Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.
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CONTENTS

722 **The Metabolic Demand and Oxygen Supply of the Heart: Physiologic and Clinical Considerations**

KARL T. WEBER and JOSEPH S. JANICKI

In the heart, unlike skeletal muscle, the conversion of chemical energy to mechanical work is highly dependent on oxidative reactions, and an oxygen debt leads to a decline in ventricular performance. This seminar reviews the physiologic principles that relate to the metabolic demand and oxygen supply in the heart and discusses their relation to the pathophysiology of the diseased heart. The major determinants of myocardial oxygen consumption ($M\dot{V}0_2$) include systolic wall force, myocardial contractile state and heart rate. All these components of ventricular contraction collectively represent the metabolic demand on the heart. The response in flow and oxygen extraction represents the metabolic reserve of the heart. The response in heart rate and blood pressure (double product) to propranolol and nitrates provides a useful clinical estimate of the reduction in $MV0_2$. Inappropriate oxygen demand relative to oxygen supply is central to patients with coronary artery disease whose oxygen delivery may be comprised and to those with chronic hemodynamic overload whose hypertrophied ventricle is failing.

730 **Myocardial Oxygen Consumption in Chronic Heart Disease: Role of Wall Stress, Hypertrophy and Coronary Reserve**

BODO-ECKEHARD STRAUER

This study of 187 patients with chronic heart disease demonstrates at least two types of inappropriate left ventricular hypertrophy and concludes that peak systolic wall stress represents a major determinant of myocardial oxygen consumption and of ventricular performance. Peak systolic wall stress is also closely related to the appropriateness of left ventricular hypertrophy, which may be defined by the relation between systolic pressure, mass to volume ratio and peak systolic wall stress. The existence of both low and high stress hypertrophy in chronic heart disease helps to explain the differences in oxygen demand and the variable results for left ventricular oxygen consumption in patients with a chronically hypertrophied heart.

741 **Temporal Relation Between Onset of Cell Anoxia and Ischemic Contractile Failure. Myocardial Ischemia and Left Ventricular Failure in the Isolated, Perfused Rabbit Heart**

WESLEY R. HARDEN, III, CLYDE H. BARLOW, MICHAEL B. SIMSON and ALDEN H. HARKEN

With high speed epicardial fluorescence photography and using reduced nicotinamide adenosine nucleotide (NADH) to identify areas of cell anoxia in the isolated perfused rabbit heart, these investigators found that ischemia is detectable within 1 to 2 seconds after coronary occlusion, that ischemic ventricular dysfunction occurs several seconds thereafter and that myocardial oxygen reserve is negligible. These data further show a close temporal relation between the onset of cell anoxia and the initiation of ventricular contractile dysfunction.

747 **Myocardial Oxygen Supply in Left Ventricular Hypertrophy and Coronary Heart Disease**

WILLIAM A. NEILL and JOAN H. FLURI-LUNDEEN

This review discusses the physiologic vascular mechanisms used by the coronary circulation in an attempt to compensate (usually only partly successful) for obstructive coronary artery disease and cardiac hypertrophy associated with excessive increases in heart work. In patients with obstructive coronary artery disease regional arteriolar dilation is utilized to compensate for local arterial stenoses. Coronary blood flow may be compensated with the patient at rest, but loss of reserve arteriolar dilation limits further adjustment to superimposed transient increases in metabolic needs. In patients with chronic aortic valve disease the metabolic rate of the left ventricle is increased in proportion to the increases in myocardial mass and work. Data are presented suggesting that angina pectoris induced by tachycardia in patients with focal coronary artery disease or with aortic stenosis is typically associated with reversible subendocardial ischemia.

DIAGNOSTIC SHELF

754 **Serial Echocardiographic Appearance of Healing Bacterial Vegetations**

ANDY STAFFORD, L. SAMUEL WANN, JAMES C. DILLON, ARTHUR E. WEYMAN and HARVEY FEIGENBAUM

Serial M mode and cross-sectional echocardiograms from six patients treated with antibiotic drugs for infectious endocarditis demonstrated that the vegetations became smaller and more echo-reflective with healing in a fol-

Continued on page A35

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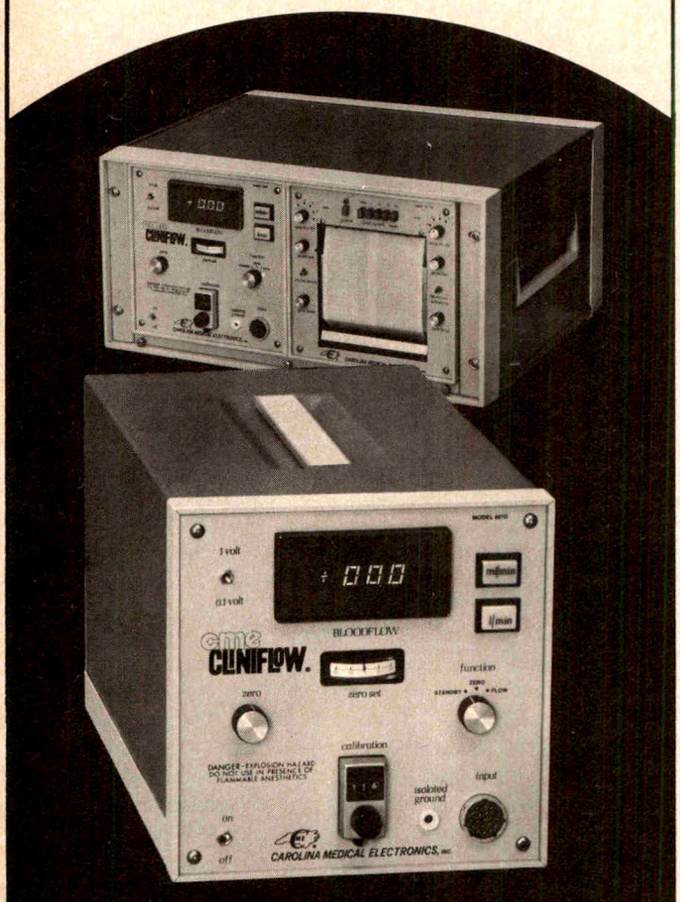

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INDICATIONS:
The prevention or correction of potassium deficit, particularly when accompanied by hypochloremic alkalosis in conjunction with thiazide diuretic therapy, in digitalis intoxication, or as the result of long-term corticosteroid therapy, low dietary intake of potassium, or excessive vomiting or diarrhea.

CONTRAINDICATIONS:
Potassium is contraindicated in severe renal impairment involving oliguria, anuria or azotemia; in untreated Addison's disease, familial periodic paralysis, acute dehydration, heat cramps, hyperkalemia from any cause. Potassium chloride should not be employed in patients receiving potassium-sparing agents such as aldosterone antagonists and triamterene.

PRECAUTIONS:
KATO is a concentrate and should be taken only after reconstituting with water as directed. This preparation, like other potassium supplements, must be properly diluted to avoid the possibility of gastrointestinal irritation. Do not use in patients with low urinary output or renal decompensation. Administer with caution; it is impossible to assess accurately the daily dose required. Excessive dosage may result in potassium intoxication. Frequent checks of the clinical status of the patient, ECG and/or plasma potassium level should be made. High plasma concentrations of potassium ion may cause death through cardiac depression, arrhythmias or arrest. Use with caution in patients with cardiac disease.

ADVERSE REACTIONS:
Vomiting, diarrhea, nausea, and abdominal discomfort may occur. Gross overdosage may produce signs and symptoms of potassium intoxication: mental confusion, listlessness, paresthesia of the extremities, weakness and heaviness of legs, flaccid paralysis, hyperkalemia, ECG abnormalities, fall in blood pressure, cardiac arrhythmias and heart block. The characteristic changes in the ECG are disappearance of the P wave, widening and slurring of QRS complex, changes of the S-T segment, tall peaked T waves, etc.

TOXICITY:
Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

TREATMENT OF HYPERKALEMIA:
1. Dextrose solution 10% or 25% containing 10 units of crystalline insulin per 20 g. dextrose, given I.V. in a dose of 300cc to 500cc in an hour. 2. Adsorption and exchange of potassium using sodium or ammonium cycle cation exchange resin, orally or as retention enema. 3. Hemodialysis or peritoneal dialysis. 4. Elimination of potassium-containing foods and medicaments. Warning: Digitalis toxicity can be precipitated by lowering the plasma potassium concentration too rapidly in digitalized patients.

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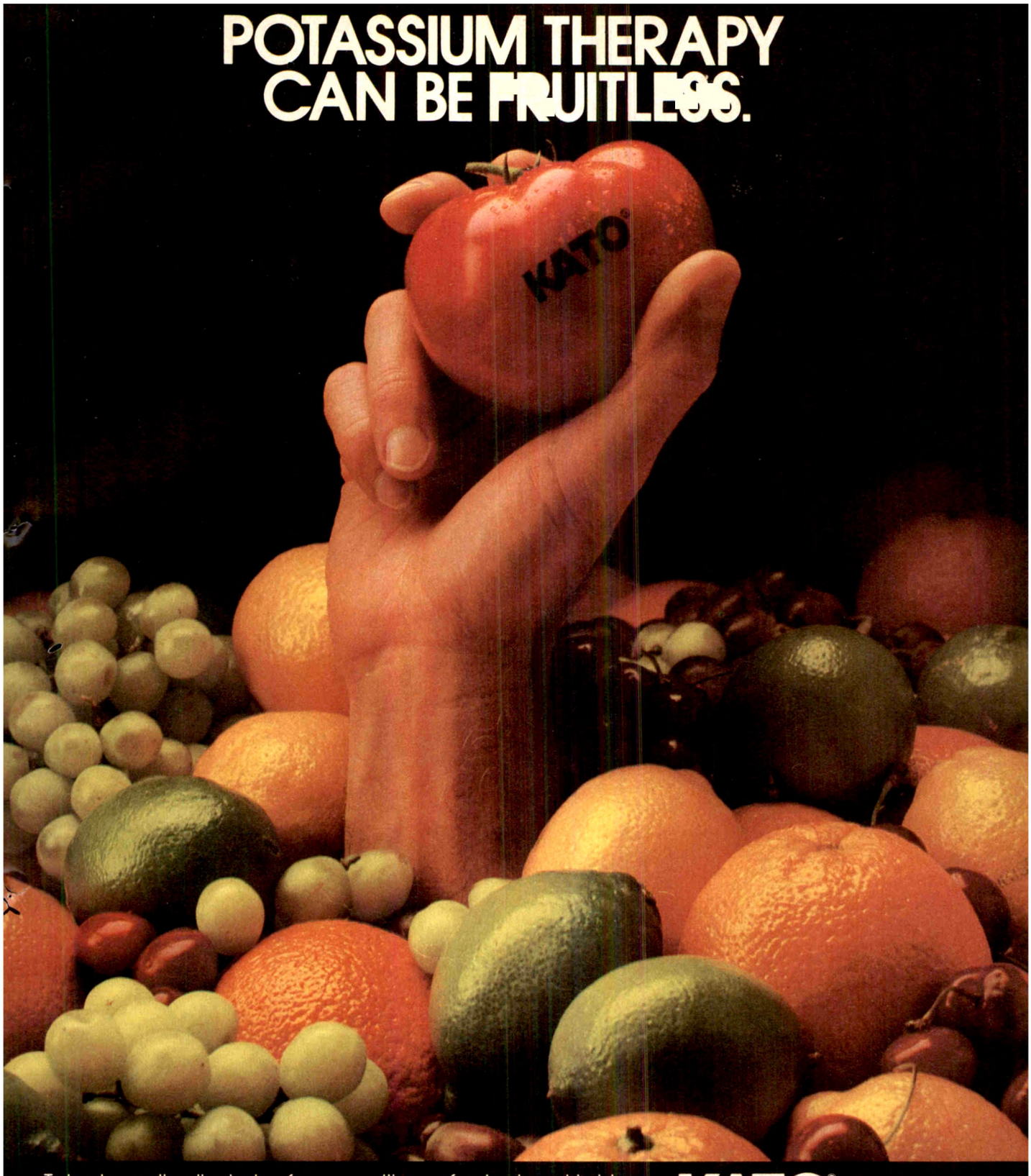

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low-up period averaging 50 weeks. M mode echocardiography was most helpful in determining the quality of echo reflection by vegetations; cross-sectional echocardiography, in judging the size and shape of a vegetation. However, failure of a vegetation to become smaller during treatment did not indicate that treatment with antibiotic drugs was unsuccessful in these patients. At present, echocardiography probably does not have resolving power sufficient to appreciate small changes in vegetations occurring during treatment and cannot be used to judge antibiotic efficacy. Nevertheless, echocardiography is the only clinical tool currently available capable of directly visualizing valve vegetations during life and is well suited to serial studies of healing vegetations in patients who do not require early valve replacement.

CASE REPORTS

761 Structural Changes in a Porcine Xenograft After Implantation for 105 Months

ROBERT M. SADE, WILLIAM B. GREENE and STANLEY M. KURTZ

Morphologic examination of a formaldehyde-fixed porcine xenograft prosthesis functioning well for 8 years and implanted for 105 months in the tricuspid valve position revealed that all leaflets suffered some gross deterioration and only one had an adherent thrombus. The principal changes in the two retracted leaflets from the implanted valve included endothelialization of connective tissue and loss of fibroblasts. The endothelium did not extend over the examined portion of the synthetic anulus of the prosthesis, suggesting that its origin was possibly from cells circulating in the blood rather than by spread from contiguous host vascular tissue.

767 Bilateral Cardiac Myxomas and Peripheral Myxomas in a Patient With Recent Myocardial Infarction

AGGIE H. M. BALK, SJOERD S. WAGENAAR and ALBERT V. G. BRUSCHKE

Myxoma is the most frequent primary tumor, constituting more than half of all cases. A 29 year old man presenting with myocardial infarction, bilateral cardiac myxomas and two myxomas elsewhere in the body highlights the need for further investigation of the metastatic spread of myxomas. Because left-sided cardiac myxoma may produce coronary embolization, myxoma has to be excluded in cases of myocardial infarction without obstructive lesions in the major branches of the coronary arteries. The diagnosis of intracardiac tumor growth in this patient was made by coronary arteriography, which showed multiple aneurysms of the distal branches of the left coronary artery and two clusters of abnormal vessels supplying tumors in the right ventricle and the left atrium.

SPECIAL DEPARTMENTS

771 Letters to the Editor

775 American College of Cardiology News

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COST IS APPROXIMATELY 20% LESS THAN OTHER LONG-ACTING QUINIDINE GLUCONATE THERAPY.†

*The quantity of drug and frequency of administration needed to achieve desired clinical results must be determined for each patient.
†Red Book, 1979.

Duraquin®
(QUINIDINE GLUCONATE TABLETS)
sustained-release tablets, 330 mg

Brief summary of prescribing information
DURAQUIN® (quinidine gluconate tablets) Sustained Release
CLINICAL PHARMACOLOGY: In clinical studies, single doses of Duraquin produced a mean maximum plasma level at 2 hours which was maintained for 12 hours. This broad plateau indicates slow, continuous absorption from the gastrointestinal tract.

In multiple dose studies, administration of Duraquin tablets, 660 mg every 12 hours, produced steady state (equilibrium) plasma levels shortly after 24 hours. The average quinidine plasma levels (Cramer and Isaksson assay[1]) were 0.81 mcg/ml and the mean peak levels were 1.16 mcg/ml in a group of normal male subjects weighing 75 Kg. Following the last dose at steady state, quinidine plasma levels decreased at an approximate rate of 50% in 10 hours. This compares to the expected plasma half-life of 6.3 hours for quinidine sulfate tablets, USP.

Therapeutic and toxic effects coordinate better with plasma levels than with dosage. While therapeutic levels of 3 to 6 mcg/ml with a range of 1.5 to 9 mcg/ml have been reported, these values are based on peak plasma levels determined by the less specific Edgar and Sokolow assay[2] This procedure yields quinidine levels averaging 22% higher than the Cramer and Isaksson assay. Plasma levels vary considerably in patients receiving identical doses. Therefore, it is advisable to adjust the dosage by monitoring plasma quinidine levels.

INDICATION: Duraquin tablets are indicated for the prevention of premature atrial, nodal, or ventricular contractions. They are also indicated for the maintenance of normal sinus rhythm following spontaneous reversion or electrical conversion of atrial, nodal, or ventricular tachycardia, atrial flutter and fibrillation (either paroxysmal or chronic).

[1]Cramer, G. and Isaksson, B. Quantitative Determination of Quinidine in Plasma. Scandinavian J. Clin. & Lab. Investigation 15, 553, 1963.
[2]Edgar, A.L. and Sokolow, M. Experiences with the Photofluorometric Determination of Quinidine in Blood. J. Lab. Clin. Med. 36, 478, 1950.

CONTRAINDICATIONS: 1. History of hypersensitivity to quinidine manifested by thrombocytopenia, skin eruption, febrile reactions, etc.
2. Complete A-V block.
3. Complete bundle branch block or other severe intraventricular conduction defects exhibiting marked QRS widening or bizarre complexes.
4. Myasthenia gravis.
5. Arrhythmias associated with digitalis toxicity.

WARNINGS: 1. (a) In the treatment of atrial fibrillation with rapid ventricular response, ventricular rate should be controlled with digitalis glycosides *prior* to administration of quinidine.
(b) In the treatment of atrial flutter with quinidine, reversion to sinus rhythm may be preceded by progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely high ventricular rate. This potential hazard may be reduced by digitalization prior to administration of quinidine.

Recent reports have described increased, potentially toxic, digoxin plasma levels when quinidine is administered concurrently. When concurrent use is necessary, digoxin dosage should be reduced and plasma concentration should be monitored and patients observed closely for digitalis intoxication.
2. Quinidine cardiotoxicity may be manifested by increased PR and QT intervals, 50% widening of QRS, and/or ventricular ectopic beats or tachycardia. Appearance of these toxic signs during quinidine administration mandates immediate discontinuation of the drug, and/or close clinical and electrocardiographic monitoring. Note: Quinidine effect is enhanced by potassium and reduced in the presence of hypokalemia.
3. "Quinidine Syncope" may occur as a complication of long-term therapy. It is manifested by sudden loss of consciousness and ventricular arrhythmias with bizarre QRS complexes. This syndrome does not appear to be related to dose or plasma levels but occurs more often with prolonged QT intervals.

Brief summary continued on following page.

PD-JA-2299-1-P (3-79)

PARKE-DAVIS

PARKE-DAVIS
Division of Warner-Lambert Company
Morris Plains, NJ 07950

Duraquin®
(QUINIDINE GLUCONATE TABLETS) sustained-release tablets, 330 mg

Brief summary continued from previous page.

4. Because quinidine antagonizes the effect of vagal excitation upon the atrium and the A-V node, the administration of parasympathomimetic drugs (choline esters) or the use of any other procedure to enhance vagal activity may fail to terminate paroxysmal supraventricular tachycardia in patients receiving quinidine.
5. Quinidine should be used with extreme caution in:
a) The presence of incomplete A-V block, since a complete block and asystole may result. Quinidine may cause unpredictable abnormalities of rhythm in digitalized hearts. Therefore, it should be used with caution in the presence of digitalis intoxication (see 1. (b) above).
b) Partial bundle branch block.
c) Severe congestive heart failure and hypotensive states due to the depressant effects of quinidine on myocardial contractility and arterial pressure.
d) Poor renal function, especially renal tubular acidosis, because of the potential accumulation of quinidine in plasma leading to toxic concentrations.

PRECAUTIONS:

1. Test Dose—A preliminary test dose of a single tablet of quinidine *sulfate* should be administered prior to the initiation of the sustained release gluconate to determine whether the patient has an idiosyncrasy to the Quinidine molecule.

2. Hypersensitivity—During the first weeks of therapy, hypersensitivity to quinidine, although rare, should be considered (eg, angioedema, purpura, acute asthmatic episode, vascular collapse).

3. Long-Term Therapy—Periodic blood counts and liver and kidney function tests should be performed during long-term therapy and the drug should be discontinued if blood dyscrasias or signs of hepatic or renal disorders occur.

4. Large Doses—ECG monitoring and determination of plasma quinidine levels are recommended when doses greater than 2.5 g/day are administered.

5. Usage in Pregnancy—The use of quinidine, in pregnancy, should be reserved only for those cases where the benefits outweigh the possible hazards to the patient and fetus.

6. Nursing Mothers—The drug should be used with extreme caution in nursing mothers because the drug is excreted in breast milk.

7. General—In patients exhibiting asthma, muscle weakness, and infection with fever *prior* to quinidine administration, hypersensitivity reactions to the drug may be masked.

DRUG INTERACTIONS:

1. Caution should be used when quinidine and its analogs are administered concurrently with coumarin anticoagulants. This combination may reduce prothrombin levels and cause bleeding.
2. Quinidine, a weak base, may have its half-life prolonged in patients who are concurrently taking drugs that can alkalize the urine, such as thiazide diuretics, sodium bicarbonate, and carbonic anhydrase inhibitors. Quinidine and drugs which alkalize the urine should be used together cautiously.
3. Quinidine exhibits a distinct anticholinergic activity in the myocardial tissues. An additive vagolytic effect may be seen when quinidine and drugs having anticholinergic blocking activity are used together. Drugs having cholinergic activity may be antagonized by quinidine.
4. Quinidine and other antiarrhythmic agents may produce additive cardiac depressant effects when administered together.
5. Quinidine interaction with cardiac glycosides (digoxin); See WARNINGS.
6. Antacids may delay absorption of quinidine but appear unlikely to cause incomplete absorption.
7. Phenobarbital and phenytoin may reduce plasma $t_{1/2}$ of quinidine by 50%.
8. Quinidine may potentiate the neuromuscular blocking effect in ventilatory depression of patients receiving decamethonium, tubocurare, or succinylcholine.

ADVERSE REACTIONS: Symptoms of cinchonism (ringing in the ears, headache, disturbed vision) may appear in sensitive patients after a single dose of the drug.

Gastrointestinal: The most common side effects encountered with quinidine are referable to this system. Diarrhea frequently occurs, but it rarely necessitates withdrawal of the drug. Nausea, vomiting, and abdominal pain also occur. Some of these effects may be minimized by administering the drug with meals.

Cardiovascular: widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms including ventricular tachycardias and fibrillation; paradoxical tachycardia, arterial embolism and hypotension.

Hematologic: acute hemolytic anemia, hypoprothrombinemia, thrombocytopenic purpura, agranulocytosis.

CNS: headache, fever, vertigo, apprehension, excitement, confusion, delirium and syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, photophobia, diplopia, night blindness, scotomata); optic neuritis.

Dermatologic: cutaneous flushing with intense pruritus.

Hypersensitivity reactions: angioedema, acute asthmatic episode, vascular collapse, respiratory arrest.

DOSAGE AND ADMINISTRATION: Dosage should be titrated to give the desired clinical effect, e.g., elimination of paroxysmal rhythm or reduction in premature contractions (See CLINICAL PHARMACOLOGY). This will often require prolonged ambulatory ECG monitoring, as hour-to-hour variability renders brief ECG recordings unreliable. When doses larger than 2.5 g/day are used, quinidine blood levels should be monitored, if possible, and serial ECGs should be followed (See WARNINGS and PRECAUTIONS).

For prevention of premature contractions and maintenance of normal sinus rhythm following spontaneous reversion or electrical conversion, the usual dosage is from 330 mg to 660 mg every eight hours, most patients requiring the higher dose.

In elderly patients, and in patients in the lower end of the normal weight range, plasma quinidine determinations should be considered. Dosage adjustments may be required.

OVERDOSAGE: Cardiotoxic effects of quinidine may be reversed in part by molar sodium lactate; the hypotension may be reversed by vasoconstrictors and by catecholamines (since the vasodilation is partly due to alpha-adrenergic blockade).

HOW SUPPLIED: N 0071-0850 (P-D 850) Duraquin (quinidine gluconate tablets) 330-mg tablets are supplied in bottles of 100 tablets.

AHFS Category 24:04

YD

PARKE-DAVIS

Division of Warner-Lambert Company
Morris Plains, NJ 07950

Brief Summary of Prescribing Information

Indications and Usage: Symptomatic relief of anxiety, tension, agitation, irritability and insomnia associated with anxiety neuroses and transient situational disturbances; anxiety associated with depressive symptoms and as a treatment of symptoms of anxiety if such symptoms are a significant feature of functional or organic disorders, particularly gastrointestinal or cardiovascular.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients on lorazepam not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation.

Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions.

Observe usual precautions with impaired renal or hepatic function.

Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component.

Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (approximately 6 times the maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatric patients requires caution and frequent monitoring for symptoms of upper G.I. disease.

Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug.

In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind that multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring of vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® (lorazepam) for Anxiety

Dosage: **Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.**

How Supplied: **0.5, 1.0 and 2.0mg tablets.**

Wyeth Laboratories
Philadelphia, PA 19101

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The anxious heart.

Since anxiety so often accompanies cardiovascular disease, you may wish to institute adjunctive therapy to help bring this complicating factor under control.

Seven benzodiazepines are now at your disposal. All of them are anxiolytics. One of them—Ativan (lorazepam)—has been specifically evaluated in seven double-blind, controlled studies involving 423 patients (211 on Ativan) and found significantly effective in the relief of anxiety associated with organic and functional cardiovascular disorders. The cardiovascular component has not, of course, been shown to be significantly benefited by such therapy.

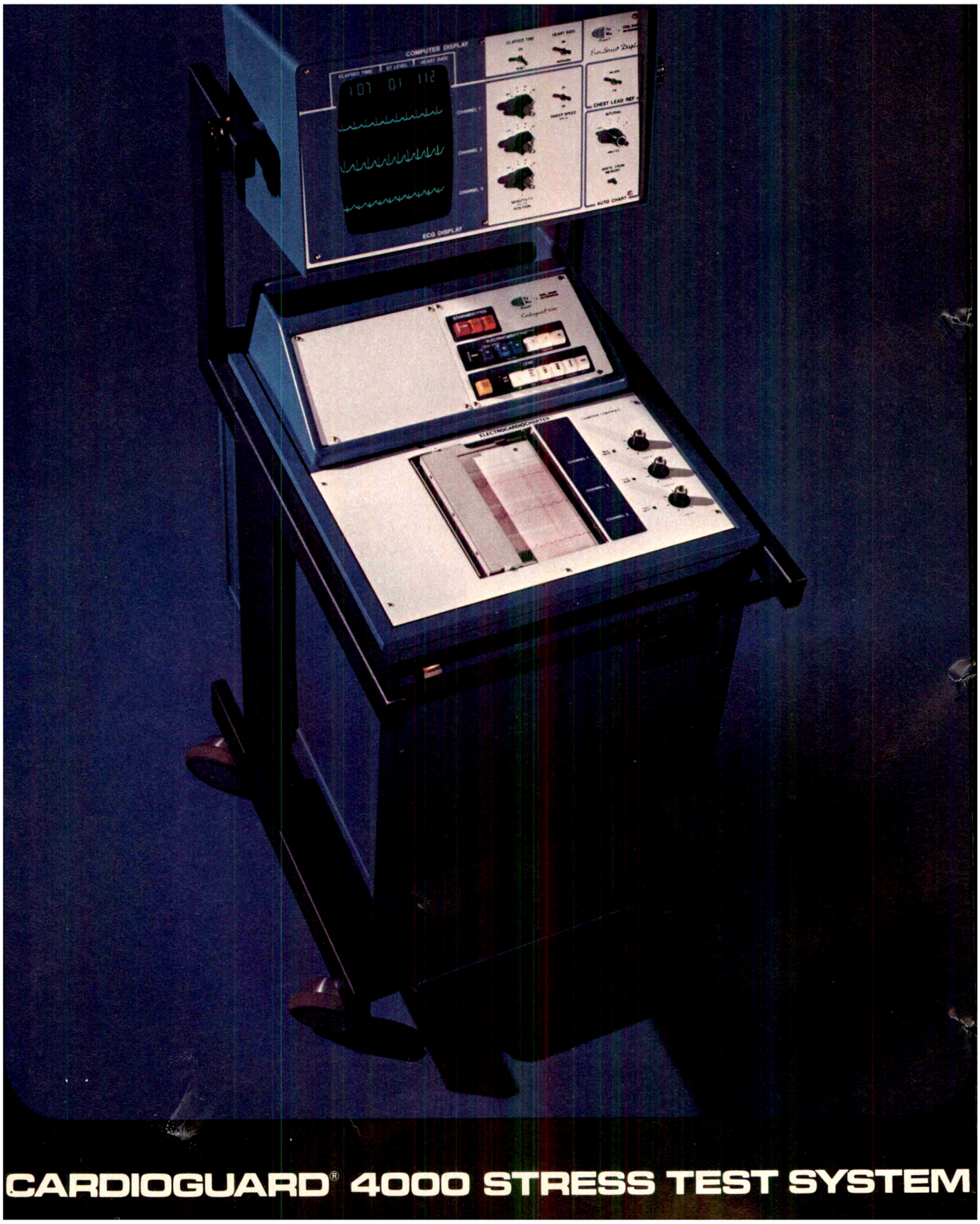
In addition to this outstanding record of clinical usefulness, Ativan offers you a unique pharmacokinetic profile. Unlike older benzodiazepines, it does not generate multiple active metabolites; steady-state serum levels are rapidly achieved and disappear rapidly once you decide to discontinue therapy. (The pharmacokinetic profile of a drug can define such characteristics as absorption, distribution, metabolism and elimination but cannot, at present, be directly related to its therapeutic effectiveness.)

Compatible with cardiotonics, antihypertensives, diuretics, anticoagulants and nonnarcotic analgesics*...usually well tolerated...simple to use on a b.i.d. schedule...a preferred prescription to control anxiety in cardiovascular disease.

*No evidence of any clinically significant interaction between Ativan and any other medication given concomitantly was observed in clinical studies. All benzodiazepines, however, including Ativan, produce added CNS depressant effects when administered with alcohol and other CNS depressants.

See important information on preceding page.

Ativan® (IV)
for (lorazepam)
Anxiety



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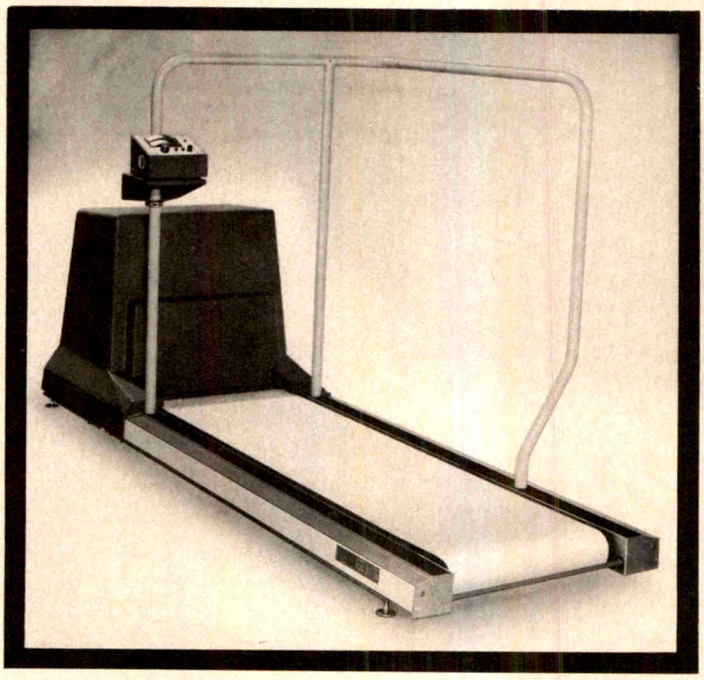

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ALDACTONE®

(spironolactone) 25 mg. tablets

WARNING

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats (see *Warnings*). Aldactone should be used only in those conditions described under *Indications*. Unnecessary use of this drug should be avoided.

Indications: Diagnosis and treatment of primary hyperaldosteronism. Essenti hypertension, edema of congestive heart failure and the nephrotic syndrome, when othe measures are considered inappropriate. Cirrhosis of the liver accompanied by edem and/or ascites. Hypokalemia.

Contraindications: Anuria, acute renal insufficiency, significant impairment of ren function, or hyperkalemia.

Warnings: Excessive potassium intake may cause hyperkalemia. Potassium sup plements should not be given with Aldactone. Do not administer concurrently with othe potassium-sparing diuretics.

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. I one study using 25, 75, and 250 times the usual daily human dose (2 mg./kg.) there was statistically significant dose-related increase in benign adenomas of the thyroid and testes In female rats there was a statistically significant increase in malignant mammary tumors a the mid-dose only. In male rats there was a dose-related increase in proliferative changes i the liver. At the highest dosage level (500 mg./kg.) the range of effects include hepatocytomegaly, hyperplastic nodules and hepatocellular carcinoma; the last was no statistically significant.

Precautions: Patients should be carefully evaluated for possible disturbances of flu and electrolyte balance. Hyperkalemia may occur in patients with impaired renal function excessive potassium intake and can cause cardiac irregularities which may be fata Hyponatremia may be caused or aggravated, especially when Aldactone is administered i combination with other diuretics. Transient elevation of BUN and/or mild acidosis ma occur. Aldactone potentiates the effect of other diuretics or antihypertensive agent particularly ganglionic blocking agents: therefore the dosage of such drugs should b reduced by at least 50 percent when adding Aldactone. Gynecomastia may develop and rare instances some breast enlargement may persist. Vascular responsiveness norepinephrine may be reduced.

Spironolactone may cross the placental barrier. Use in pregnant women requires that th anticipated benefit be weighed against possible hazard to the fetus. Breast feeding shou be discontinued when Aldactone is being used.

Adverse Reactions: Gynecomastia is observed not infrequently. Gastrointestinal sym toms including cramping and diarrhea, drowsiness, lethargy, headache, maculopapular erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, inabili to achieve or maintain erection, irregular menses or amenorrhea, postmenopaus bleeding, hirsutism and deepening of the voice. Carcinoma of the breast has been reporte but a cause-and-effect relationship has not been established. Adverse reactions ar usually reversible upon discontinuation of the drug.

Dosage and Administration

For primary hyperaldosteronism: 400 mg. daily for three to four weeks (long test), for four days (short test). For preparation for surgery or for long-term maintenance therap 100 to 400 mg. daily.

For edema in adults: Initial daily dosage is 100 mg. in divided doses but may range fro 25 to 200 mg. daily. If after five days an adequate diuretic response has not occurred, second diuretic which acts more proximally in the renal tubule may be added. The dosag of Aldactone should remain unchanged when other diuretic therapy is added.

For edema in children: Initial daily dosage should provide approximately 1.5 mg. p pound of body weight (3.3 mg./kg.) in divided doses.

For essential hypertension: Initial adult daily dosage of 50 to 100 mg. in divided dose alone or with diuretics which act more proximally in the renal tubule, or with oth antihypertensive agents. Continue treatment for at least two weeks since maxim response may not occur before this time. Adjust subsequent dosage according to patie response.

For hypokalemia: 25 to 100 mg. daily in divided doses.

SEARLE **Searle & Co.**
San Juan, Puerto Rico 00936

Address medical inquiries to:
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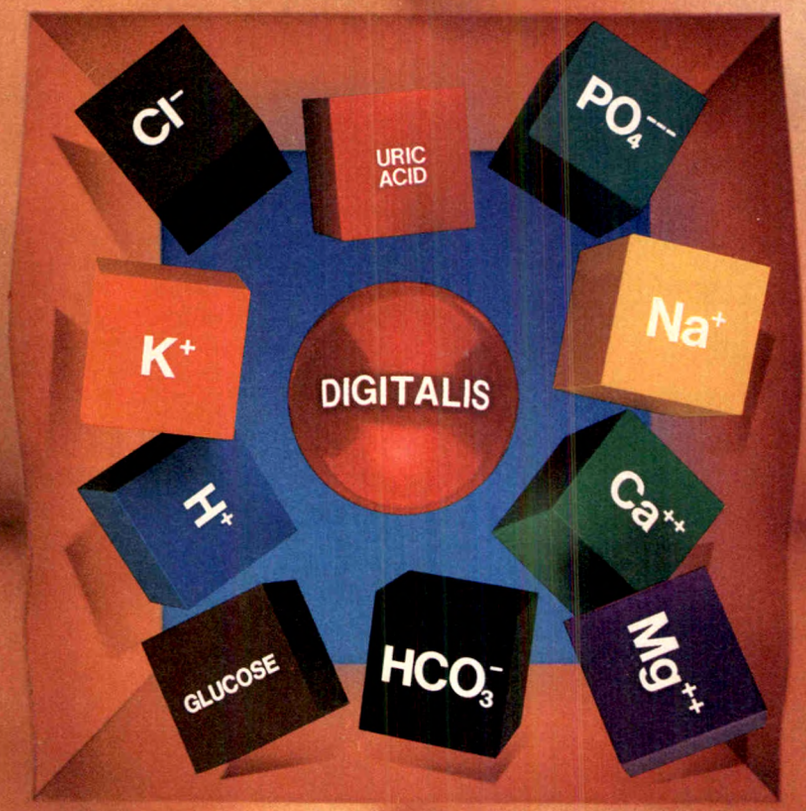
8

The delicate balance during treatment of CHF



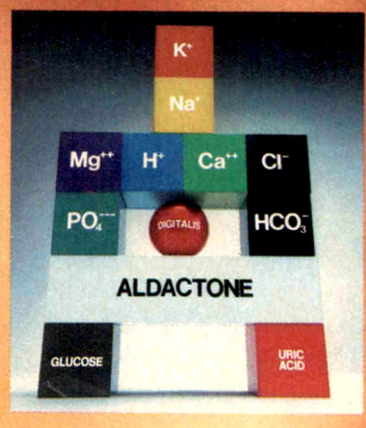
Electrolyte imbalance is often a problem during digitalis therapy and most diuretics can worsen the problem. With both the thiazides and furosemide, fluid and electrolyte imbalance may lead to digitalis toxicity.

Aldactone for concomitant digitalis/diuretic therapy.

Aldactone® (spironolactone) provides gradual and sustained diuresis and, through a unique mechanism, helps prevent hypokalemia with limited risk of hyperkalemia. *Plus* . . . Aldactone does not adversely affect serum calcium, magnesium, and uric acid levels nor alter glucose tolerance.

Limitations to consider.

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. Thus Aldactone should be prescribed only when other measures are considered inadequate or inappropriate. (See boxed warning and *Warnings* section of Aldactone prescribing information, a brief summary of which appears on the facing page.)



SEARLE

Aldactone®

(spironolactone) 25-mg. tablets

The diuretic that helps maintain the delicate balance of electrolytes . . . when other measures are considered inadequate or inappropriate.

Before prescribing, please consult the complete prescribing information, a brief summary of which appears on the facing page.

Where would you keep it?

Let's assume that you have just taken delivery of a beautiful new Lifepak 6 defibrillator/monitor—state of the art, the best there is.

Now then, where do you keep it?

In the Emergency Department? CCU? OR? Intensive Care? Radiology? Special Procedures? They *all* should have a defibrillator/monitor close at hand. And of course, with a building full of sick people, you must face the fact that it's quite possible for cardiac emergency to strike anywhere—any room, any floor, any time.

We hope we've made our point: It's both prudent and wise to make sure your hospital has *enough* defibrillator/monitors. And one very nice feature of our new two-part Lifepak 6 acute cardiac care system is that you can equip yourself with any combination of defibrillators and monitors that may be called for.

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INDICATIONS:

1. Congestive heart failure: Congestive heart failure, all degrees, is the primary indication. The increased cardiac output due to digoxin results in diuresis and general amelioration of the disturbances characteristic of right (venous congestion, edema) and left (dyspnea, orthopnea, cardiac asthma) heart failure.

Digoxin, generally, is most effective in "low output" failure and less effective in "high output" (bronchopulmonary insufficiency, infection, hyperthyroidism) heart failure.

Digoxin should be continued after heart failure is abolished unless some known precipitating factor is corrected.

2. Atrial fibrillation: Atrial fibrillation, especially when the ventricular rate is elevated. Digoxin rapidly reduces ventricular rates and eliminates the pulse deficit. Palpitation, precordial distress or weakness are relieved and any concomitant congestive failure ameliorated. Digoxin should be continued in doses necessary to maintain the desired ventricular rate and other clinical effects.

3. Atrial flutter: Digoxin slows the heart and regular sinus rhythm may appear. Frequently the flutter is converted to atrial fibrillation with a slow ventricular rate. Stopping digoxin at this point may be followed by restoration of sinus rhythm, especially if the flutter was of the paroxysmal type. It is preferable, however, to continue digoxin if failure ensues or if atrial flutter is a frequent occurrence.

4. Paroxysmal atrial tachycardia: Oral digoxin may be used, especially if the condition is resistant to lesser measures. Depending on the urgency, a more rapid acting parenteral preparation may be preferable to initiate digitalization, although if heart failure has ensued or paroxysms recur frequently, digoxin should be maintained by oral administration.

Digoxin is not indicated in sinus tachycardia unless due to heart failure.

5. Cardiogenic shock: The drug is often employed, especially when the condition is accompanied by pulmonary edema. Digoxin seems to affect adversely shock due to septicemia from gram-negative bacteria.

CONTRAINDICATIONS: The presence of toxic effects (see ADVERSE REACTIONS section) induced by any digitalis preparation is a contraindication to all of the glycosides.

Allergy, though rare, does occur. It may not extend to all preparations, and another may be tried.

Ventricular fibrillation.

WARNINGS:

> Digitalis alone or with other drugs has been promoted for use in the treatment of obesity. This use of digoxin or other digitalis glycosides is unwarranted. Moreover, since they may cause potentially fatal arrhythmias or other adverse effects, the use of these drugs in the treatment of obesity is dangerous.

Many of the arrhythmias for which digoxin is advised closely resemble those reflecting digoxin intoxication. If the possibility of digoxin intoxication cannot be excluded, cardiac glycosides should be temporarily withheld if permitted by the clinical situation.

The patient with congestive heart failure may complain of nausea and vomiting. These symptoms may also be indications of digoxin intoxication. A clinical determination of the cause of these symptoms must be attempted before further drug administration.

Patients with renal insufficiency require smaller than usual doses of digoxin. Newborn infants display considerable variability in their tolerance to digoxin, depending on their degree of maturity.

Premature and immature infants are particularly sensitive, and dosage must be reduced and digitalization should be even more individualized and cautiously approached than in more mature infants. Impaired renal function must also be carefully taken into consideration.

Congestive heart failure accompanying acute glomerulonephritis requires extreme care in digitalization. A relatively low total dose administered in divided doses and concomitant use of antihypertensive drugs has been recommended. ECG monitoring is essential. Digoxin should be discontinued as soon as possible.

Patients with idiopathic hypertrophic subaortic stenosis must be managed extremely carefully. Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.

Patients with rheumatic carditis, especially when severe, are unusually sensitive to digoxin and prone to disturbances of rhythm. If heart failure develops, digitalization may be initiated with relatively low doses, then it can be cautiously increased until a beneficial effect is obtained. If a therapeutic trial does not result in improvement, the drug should be considered ineffective and be discontinued.

Note: Digitalis glycosides are an important cause of accidental poisoning in children.

PRECAUTIONS: Atrial arrhythmias associated with hypermetabolic states are particularly resistant to digoxin treatment. Care must be taken to avoid digoxin toxicity if digoxin is used to help the arrhythmia.

Digoxin is not indicated for the treatment of ventricular tachycardia unless congestive heart failure supervenes after a protracted episode not itself due to digoxin.

Potassium depletion sensitizes the myocardium to digoxin and toxicity may develop even with usual dosage. Hypokalemia may also alter the rate of onset and intensity of the positive inotropic effect of digoxin. Therefore, it is desirable to maintain normal serum potassium levels in patients being treated with digoxin.

Potassium wastage may result from diuretic or corticosteroid therapy, hemodialysis, and from suction of gastrointestinal secretions. It may accompany malnutrition, diarrhea, prolonged vomiting, old age, and long-standing congestive heart failure. In general, rapid changes in serum potassium or other electrolytes are to be avoided, and intravenous treatment with potassium should be reserved only for special circumstances as described below (see TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGES section).

Patients with acute myocardial infarction, severe pulmonary disease, or far advanced heart failure may be more sensitive to digoxin and more prone to disturbances of rhythm.

Calcium affects contractility and excitability of the heart in a manner similar to that of digoxin. Calcium may produce serious arrhythmias in digitalized patients.

In myxedema, the digoxin requirements are less because excretion rate is decreased and blood levels are significantly higher.

In incomplete A-V block, especially in patients subject to Stokes-Adams attacks, advanced or complete heart block may develop if digoxin is given. Heart failure in these patients can usually be controlled by other measures and by increasing the heart rate.

Patients with chronic constrictive pericarditis may respond unfavorably to digoxin.

Patients with idiopathic hypertrophic subaortic stenosis must be managed extremely carefully. Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.

Renal insufficiency delays the excretion of digoxin and dosage must be adjusted accordingly in patients with renal disease. Note: This applies also to potassium administration should it become necessary.

Electrical conversion of arrhythmias may require reduction of digoxin dosage.

Dosage must be carefully titrated and differences in the bioavailability of parenteral preparations, elixirs, and tablets should be taken into account when switching patients from one preparation to another.

Electrocardiographic monitoring may be necessary to avoid intoxication.

Premonitory signs of toxicity in the newborn are undue slowing of the sinus rate, sinoatrial arrest, and prolongation of PR interval.

ADVERSE REACTIONS:

Gynecomastia: Uncommon.

Overdose or toxic effects in adults:

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea are the most common early symptoms of overdosages in the adult (but rarely conspicuous in infants). Uncontrolled heart failure may also produce such symptoms.

Central nervous system: Visual disturbances (blurred vision, yellow vision), headache, weakness, apathy.

Cardiac disturbances (arrhythmias): Ventricular premature beats are the most common, except in infants and young children. Paroxysmal and nonparoxysmal nodal rhythms, atrioventricular (interference) dissociation and paroxysmal atrial tachycardia (PAT) with block are also common arrhythmias due to digoxin overdosage.

Conduction disturbances: Excessive slowing of the pulse is a clinical sign of digoxin overdosage. Atrioventricular block of increasing degree may proceed to complete heart block. Note: The electrocardiogram is fundamental in determining the presence and nature of these cardiac toxic disturbances. Digoxin may also induce other changes (as of the ST segment), but these provide no measure of the degree of digitalization.

Overdose or toxic effects in children:

Toxic signs differ from the adult in a number of respects. Cardiac arrhythmias are the more reliable and frequent signs of toxicity.

Vomiting and diarrhea, neurologic and visual disturbances are rare as initial signs.

Premature ventricular systoles are rarely seen; nodal and atrial systoles are more frequent.

Atrial arrhythmias, atrial ectopic rhythms, and paroxysmal atrial tachycardia with A-V block particularly are more common manifestations of toxicity in children.

Ventricular arrhythmias are rare.

TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGE: Digoxin should be discontinued until all signs of toxicity are abolished. Discontinuation may be all that is necessary if toxic manifestations are not severe and appear after the time for peak effect of the drug.

Potassium salts are commonly used. Potassium chloride in divided oral doses totaling 4-6 grams for adults (see PEDIATRIC INFORMATION section for pediatric dosage) may be given provided renal function is adequate.

When correction of the arrhythmia is urgent and the serum potassium level is low or normal, potassium should be administered intravenously in a solution of 5 percent dextrose in water. A total of 40-100 milliequivalents (30 milliequivalents per 500 milliliters) is given at the rate of 20 milliequivalents per hour unless limited by pain due to local irritation.

Additional amounts may be given if the arrhythmia is uncontrolled and the potassium well tolerated.

Continuous electrocardiographic monitoring should be performed to watch for any evidence of potassium toxicity, e.g., peaking of T waves, and to observe the effect on the arrhythmia so that the infusion may be promptly stopped when the desired effect is achieved.

Caution: Potassium should not be used and may be dangerous for severe or complete heart block due to digoxin and not related to any tachycardia.

Other agents that have been approved for the treatment of digoxin intoxication include procainamide, lidocaine, and propranolol.

Pediatric Information: (See adult section for other recommendations for the treatment of arrhythmias produced by overdosages and for additional recommendations and cautions regarding the use of potassium.) Potassium preparations may be given orally in divided doses totaling 1-1.5 milliequivalents/kilogram (1 gram K contains 13.4 milliequivalents). When correction of the arrhythmia is urgent, approximately 0.5 milliequivalents/kilogram of potassium per hour may be given, with careful electrocardiographic monitoring, as a solution of 20 milliequivalents or less for 500 milliliters in 5 percent dextrose in water. The total dose should generally not exceed 2 milliequivalents of potassium/kilogram.

DOSAGE AND ADMINISTRATION: Oral digoxin is administered slowly or rapidly as required until the desired therapeutic effect is obtained without symptoms of overdosage. The amount can be predicted approximately from the lean body mass of the patient with allowances made for excretion during the time taken to induce digitalization.

Subsequent maintenance dosage is also determined tentatively by the amount necessary to sustain the desired therapeutic effect.

Recommended dosages are practical average figures that may require considerable modification as dictated by individual sensitivity or associated conditions. Diminished renal function is the most important factor requiring modification of recommended or average doses. (See WARNINGS and PRECAUTIONS sections.)

The average amount of digoxin that patients must accumulate to be digitalized with digoxin tablets is 1.0-1.5 milligrams. Digitalization may be accomplished by any of several approaches that vary in dosage and frequency of administration, but reach the same endpoint in terms of total amount accumulated.

In previously undigitalized patients, a single loading dose of 0.5-0.75 milligram orally usually produces a detectable effect in 1-2 hours that becomes maximal in 6-8 hours. Additional doses of 0.25-0.5 milligram may be given cautiously at 6-8 hour intervals to full digitalization.

In previously undigitalized patients, institution of daily maintenance therapy (0.125-0.5 milligram, see next paragraph) without a loading dose results in development of steady-state plateau concentrations in about 7 days in patients with normal renal function.

The average daily oral maintenance dose is 0.125-0.5 milligram, usually 0.25 milligram. In the elderly patient, 0.125-0.25 milligram should be considered the average maintenance dose.

In patients with renal impairment, digoxin excretion is impaired and serum half-life is prolonged. Digitalizing and maintenance doses are lower than those recommended for patients with normal renal functions. Signs of digoxin toxicity develop sooner in patients with renal impairment, and it takes longer for toxic signs and symptoms to disappear. Because of the prolonged half-life, a longer period of time is required to achieve an initial or new steady-state plateau in patients with renal impairment than in patients with normal renal function.

It cannot be overemphasized that the values given are averages and substantial individual variation can be expected.

Children: Digitalization must be individualized. Generally, premature and immature infants are particularly sensitive, requiring reduced dosage that must be determined by careful titration.

Oral Dosage. Beyond the immediate newborn period, children require proportionally greater doses than adults on the basis of body weight or surface area. The recommended oral digitalizing dosages in children with normal renal function are:

Newborn infants (normal), up to 1 month, require 40-60 micrograms (mcg)/kilogram.
Infants, 1 month to 2 years, require approximately 60-80 micrograms (mcg)/kilogram.
Children, 2 years to 10 years, require 40-60 micrograms (mcg)/kilogram.
Children, over 10 years of age, require adult dosages in proportion to their body weight.
Maintenance therapy is 20-30 percent of the digitalizing dose administered each day.

Long term use of digoxin is indicated in almost all infants who have been digitalized for acute congestive heart failure unless the cause is transient. Many favor maintaining digoxin until at least 2 years of age in all infants with paroxysmal atrial tachycardia or in those who show either definite or latent failure.

Many children with severe inoperable congenital defects need digoxin throughout childhood and often for life.

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CLINICAL STUDIES

Serial Noninvasive Assessment of Left Ventricular Hypertrophy And Function After Surgical Correction of Aortic Regurgitation

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Serial echocardiographic analyses of left ventricular hypertrophy and function, with validation of extent of shortening by first pass radionuclide angiography, was performed in 16 patients before and after surgical correction of severe aortic valve regurgitation. All patients were symptomatic (predominantly in New York Heart Association functional class III or IV) before operation but were in class I or II after operation. The preoperative pattern of eccentric hypertrophy (increased mass with normal ratio of left ventricular cross-sectional wall area to cavity area) changed immediately after operation to a pattern of concentric hypertrophy (increased mass with increased ratio of left ventricular cross-sectional wall area to cavity area) because of a significant reduction in chamber size and increase in wall thickness. On late follow-up (9 to 35 months, average 15 months after operation), the hypertrophy lessened significantly, the cross-sectional area of the ventricular wall decreasing to 21.1 ± 5.4 (mean ± standard deviation) cm^2 from a preoperative average of 31.6 ± 4.8 cm^2 ($P < 0.01$), and the ratio of wall area to cavity area was once again normal. In the same period, left ventricular end-diastolic diameter decreased from 6.52 ± 0.68 to 4.64 ± 0.52 cm ($P < 0.01$). Preoperatively, ejection phase indexes were normal or only marginally depressed in 12 of 16 patients but were moderately depressed in the remaining 4. At early follow-up (average 4 months) ventricular shortening tended to increase; and at late follow-up the fractional shortening of the minor axis, the ejection fraction and the mean velocity of circumferential fiber shortening increased to 0.39 ± 0.07, 0.68 ± 0.10 and 1.26 ± 0.22 circumference/sec, respectively, from preoperative values of 0.33 ± 0.09, 0.60 ± 0.14 and 1.05 ± 0.31 circumferences/sec ($P < 0.05$ for each index). In the four subjects with preoperative depression of left ventricular function, the extent and speed of myocardial shortening at late follow-up became normal in three subjects and remained moderately depressed in one patient. Paradoxical septal motion was observed immediately postoperatively and in the early follow-up studies, but it was noted in only 3 of 16 cases by the late follow-up period. Provided septal dyskinesia was not present, echocardiographic and first pass radionuclide determinations of ejection fraction correlated highly ($r = 0.92$).

It is concluded that when aortic valve replacement for symptomatic aortic regurgitation is undertaken prior to severe myocardial decompensation, improvement in clinical status is associated with significant regression of myocardial hypertrophy, reduction in left ventricular size, evolution of a normal mass/volume ratio, recovery of septal dyskinesia as revealed on echocardiography, and improvement in left ventricular function. These data do not define the type and degree of left ventricular dysfunction which is irreversible.

From the Cardiovascular Division, Department of Medicine, and Division of Nuclear Medicine, Department of Radiology, University of California at San Diego, and Naval Regional Medical Center, San Diego, California. This project was supported by Research Grant HL12373 awarded by the National Heart, Lung, and Blood Institute, The National Institutes of Health, Bethesda, Maryland. Manuscript received June 22, 1978; revised manuscript received and accepted May 16, 1979.

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Properly selected patients undergoing prosthetic cardiac valve replacement for aortic regurgitation generally experience relief of clinical symptoms.[1–6] Less well documented are the associated alterations of the extent and pattern of left ventricular hypertrophy and function after valve replacement. Previous reports on left ventricular performance after correction of aortic regurgitation have generally been influenced by studies in patients who underwent cardiac catheterization because their postoperative course did not follow the expected pattern.[4,7,8] Serial noninvasive assessment of left ventricular function in unselected patients should provide a better definition of the reversibility of myocardial adaptations and dysfunction accompanying this chronic volume overload and should give insight into the postoperative mechanical changes that are associated with symptomatic improvement.

In this study we analyzed left ventricular hypertrophy and function serially with echocardiography in a group of patients with predominant aortic regurgitation who underwent aortic valve replacement. The diagnostic methods used correlate highly with left ventriculography, while allowing repetitive studies of left ventricular size and mass over many months without risk of mortality. Thus, we studied these patients both early and late in their recovery course and at a time when cardiac catheterization was not indicated.

Methods

Patient Selection

Sixteen patients, eight men and eight women, undergoing aortic valve replacement for chronic aortic insufficiency formed the study population (Table I). Patients were entered into the study in sequence, selection being limited by the willingness of the individual subjects to participate in the follow-up studies and the technical adequacy of the serial diagnostic tests. Preoperatively, 13 patients were in functional class III (New York Heart Association classification[9]), 2 patients in class IV and one in class II. Thus, 15 of 16 subjects complained of reduced exercise tolerance or significant dyspnea, or both, with less than ordinary activity. One patient (Case 12) complained of weakness and mild dyspnea at rest, and one (Case 10) noted symptoms with ordinary physical activity only. Postoperatively all patients had symptomatic improvement and were judged to be in class I or II. Except in two patients (Cases 8 and 16) the standard chest X-ray film showed an increased cardiothoracic ratio preoperatively (mean 0.57, range 0.48 to 0.63). In 14 of the 16 patients the standard 12 lead electrocardiogram demonstrated left ventricular hypertrophy according to the criteria of Estes et al.[10]

Cardiac catheterization and angiography: Preoperative evaluation with left heart catheterization and angiography was performed using standard methods. Left ventricular angiographic images at end-diastole and end-systole were determined with planimetry on an electromagnetic tablet, and left ventricular volumes were calculated using the regression formula of Dodge et al.[11] for anteroposterior and lateral biplane studies. Absolute left ventricular volume data were available for only about half of the patients because one of the three participating cardiac catheterization laboratories did not use a calibration grid for magnification factors. Mean velocity of circumferential shortening, as an ejection phase index of basal ventricular function, was calculated from the left ventriculogram according to previously published methods.[12] All patients manifested a uniform pattern of contraction without segmental wall motion abnormalities on left ventricular cineangiography. No patient had evidence of signifi-

TABLE I

Clinical, Hemodynamic and Angiocardiographic Findings, Type of Surgery and Valve Prosthesis

Case no.	Age (yr) & Sex	NYHA Class	ECG	CTR	LVEDP	AoP S	AoP D	CI	EF	Mean Vcf	EDVI	Aortic Valve Prosthesis	Prosthetic Valve Size [mm]
1	22M	III	LVH	0.56	16	120	36	3.0	0.64	1.07	251	PHG	27
2	46F	III	LVH	0.57	45	200	48	. . .	0.36	. . .	. . .	PHG	25
3	27F	III	0	0.62	13	130	78	3.5	0.69	1.17	139	PHG	27
4	54M	III	LVH	0.54	10	120	58	3.6	0.69	1.28	140	PHG	29
5	62F	III	LVH	0.63	11	128	62	3.1	0.34	0.48	148	PHG	23
6	79M	IV	LVH	0.55	30	124	40	2.2	0.58	1.31	120	PHG	25
7	23F	III	LVH	0.54	23	200	80	2.7	0.73	1.78	. . .	PHG	25
8	46F	III	LVH	0.50	15	150	70	2.6	0.73	1.94	. . .	BS	21
9	51F	III	LVH	0.59	9	132	54	3.5	0.54	1.07	. . .	BS	23
10	11M	II	LVH	0.57	20	120	63	3.5	0.74	1.41	. . .	PHG	25
11	64M	III	LVH	0.55	11	120	59	2.6	. . .	. . .	. . .	PHG	27
12	44F	IV	LVH	0.62	22	200	72	2.1	0.42	0.70	169	PHG	27
13	24F	III	LVH	0.63	16	142	58	2.8	0.59	1.18	227	HMG	22
14	63M	III	LVH	0.55	34	155	70	2.5	0.47	0.78	. . .	PHG	27
15	61M	III	0	0.58	. . .	171	52	3.5	. . .	. . .	. . .	PHG	27
16	30M	III	LVH	0.48	28	94	38	2.8	0.55	1.03	103	PHG	29
no.	16			16	15	16	16	15	14	13	8		
Mean	44.2			0.47	20.2	144.1	58.6	2.9	0.58	1.17	162		
SD	19.4			0.04	10.3	32.7	13.6	0.5	0.14	0.40	53		
SE	4.9			0.01	2.7	8.2	3.4	0.1	0.04	0.11	18		

AoP = aortic pressure (mm Hg); BS = Bjork-Shiley prosthesis; CI = cardiac index (liters/min per m2); CTR = cardiothoracic ratio; D = diastolic; ECG = electrocardiogram; EDVI = end-diastolic volume index (m1/m2); EF = angiocardiographic ejection fraction; LVH = left ventricular hypertrophy; HMG = free aortic homograft; LVEDP = left ventricular end-diastolic pressure (mm Hg); no. = number of patients; NYHA = New York Heart Association; PHG = porcine heterograft; S = systolic; SD = standard deviation; SE = standard error; Vcf = mean velocity of minor axis shortening (end-diastolic dimension/sec).

cant coronary artery disease on selective coronary arteriography. All patients had grade 3+ or 4+ aortic regurgitation as previously defined,[13] on supravalve aortography. All had transvalve pressure gradients during systole of less than 10 mm Hg. One patient (Case 5) had associated mitral stenosis (mean pressure gradient from the left atrium to the left ventricle of 7 mm Hg) for which the cardiac surgeon made an intraoperative decision to perform a mitral commissurotomy.

Prosthetic valve replacement: The aortic valve was replaced by a Hancock porcine heterograft in 13 patients, by a Bjork-Shiley tilting disc prosthesis in 2 patients and by a free aortic homograft in 1 patient. The porcine heterografts inserted had an average size of 26.3 mm, and only one patient received a heterograft smaller than 25 mm. Because small porcine heterografts can produce considerable systolic gradients,[14,15] a Bjork-Shiley prosthesis or a free aortic homograft was utilized in patients with a small aortic root.

Noninvasive procedures: An echocardiogram, a 12 lead electrocardiogram and a chest roentgenogram were obtained preoperatively, at the time of hospital discharge, at average intervals of 4.3 months (range 3 to 6 months) and 15.2 months (range 9 to 35 months) after valve replacement. When first pass radionuclide angiography became available at our institution, an effort was made to perform this examination as well, in order to corroborate the echocardiographic determination of left ventricular ejection fraction.

Evaluation of Left Ventricular Size, Mass and Function

Echocardiography: The serial echocardiograms were recorded with a Picker ultrasonoscope utilizing a 2.25 megahertz or a 1.6 megahertz transducer focused at 7.5 cm or 10 cm, respectively; the output signal was recorded on a Honeywell Visicorder oscillograph, model 1856, or on an IREX recorder. All serial echocardiograms were obtained with the subject in the same position, either the supine or partial left lateral decubitus posture. The transducer was placed in the third or fourth intercostal space immediately to the left of the sternum. With the transducer directed posteriorly and slightly medially, the mitral valve was identified; the transducer was then rotated inferolaterally to obtain echoes from the endocardial surface and the left side of the interventricular septum. When scanning was performed medially and superiorly, care was taken to identify and measure the greatest dimension of the left ventricular minor axis at tthe level of the posterior mitral leaflet supporting apparatus. At this transducer orientation, fragments of the mitral valve leaflet were also frequently observed. The epicardium was identified by progressive damping of the echographic signal (Fig. 1, right).

Left ventricular dimensions: Left ventricular minor axis dimension was measured between the endocardial surface of the posterior wall and the interventricular septum. End-diastolic dimension (EDD) was taken at the peak of the R wave of the simultaneously recorded electrocardiogram. End-systolic dimension (ESD) was defined as the minimal distance separating the endocardial surfaces at points directly opposing each other and occurring before the dicrotic notch of the carotid pulse tracing. End-diastolic posterior wall thickness was measured from the leading edge of the endocardium to the leading edge of the epicardium at the peak of the R wave of the electrocardiogram (Fig. 1).

For measurement of the systolic ejection period, a simultaneous carotid pulse tracing was recorded by a bell held manually over the carotid artery and connected by an air-filled tube to a Statham P23Db strain gauge manometer. In the majority of observations left ventricular ejection time (LVET) was taken from this simultaneous carotid pulse tracing. Occasionally, a carotid pulse tracing was not available and left ventricular ejection time was measured from the peak of the R wave to the maximal anterior excursion of the posterior wall, less 50 msec for the preejection period. This method was compared with the carotid pulse wave technique in 10 patients before and after valve replacement; both methods of calculating left ventricular ejection time yielded nearly identical results.

Fractional shortening of the minor axis ($\Delta d/EDD$) *was calculated as:*

$$\Delta d/EDD = (EDD - ESD)/EDD \quad (1)$$

The mean normalized shortening velocity of the minor diameter of the ventricular chamber [also commonly reported as mean velocity of circumferential fiber shortening or mean Vcf[12]] was calculated as:

$$mVcf = (EDD - ESD)/(EDD \times LVET) \quad [EDD \times sec^{-1}]. \quad (2)$$

End-diastolic volume (*EDV*) *and end-systolic volume* (*ESV*) were estimated from echocardiographic measurements

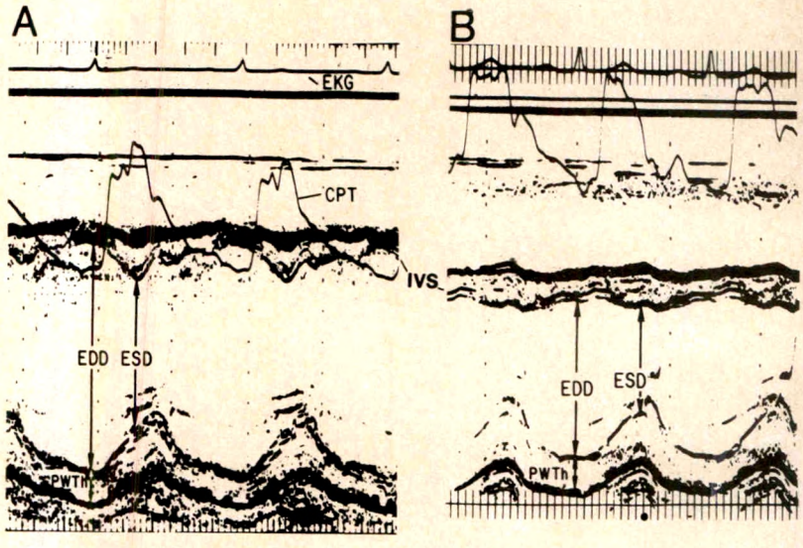

FIGURE 1. Echocardiogram before (**left**) and after (**right**) correction of severe aortic regurgitation. **Left,** before valve replacement, note the marked increase in ventricular size and left ventricular wall cross-sectional area (CSA) (EDD 7.3 cm, PWTh 1.10 cm, CSA 29.0 cm^2) and normal left ventricular performance (ejection fraction 0.62, mean Vcf 1.07 EDD sec^{-1}). **Right,** 1 year after aortic valve replacement, there is now normal ventricular size (EDD 4.76 cm) and reduction of LV-CSA by 34 percent (PWTh 1.05 cm, CSA 19.2 cm^2); left ventricular performance is unchanged (ejection fraction 0.63, mean Vcf 1.13 EDD sec^{-1}). CPT = carotid pulse tracing; EDD = end-diastolic dimension; ECG = electrocardiogram; ESD = end-systolic dimension; IVS = interventricular septum; PWTh = posterior wall thickness.

using the regression formulas of Teichholz et al.,[16] where

$$EDV = 7/(2.4 + EDD) \times (EDD)^3 \quad [ml]. \tag{3}$$

$$ESV = 7/(2.4 + ESD) \times (ESD)^3 \quad [ml]. \tag{4}$$

Ejection fraction (*EF*) was calculated from these volume estimates as:

$$EF = EDV - ESV/EDV \ [\%]. \tag{5}$$

Normalized septal velocity (*NSV*) *and normalized posterior wall velocity* (*NPWV*) were calculated from left ventricular ejection time, end-diastolic diameter, and septal motion (SM) or posterior wall motion (PWM):

$$NSV = SM/(LVET \times EDD) \quad [EDD \times sec^{-1}]. \tag{6}$$

$$NPWV = PWM/(LVET \times EDD) \quad [(EDD \times sec^{-1})]. \tag{7}$$

Left ventricular mass: *Left ventricular cross-sectional wall area* (*CSA*) (*Fig. 2*), used as an index of left ventricular mass, was calculated from posterior wall thickness (PWTh) and end-diastolic dimension by subtracting the cross-sectional area of the left ventricular cavity from the total cross section of the left ventricle according to the following formula:

$$CSA = \pi(EDD/2 + PWTh)^2 - \pi(EDD/2)^2 \quad [cm^2]. \tag{8}$$

This computation assumes that the contributions of septal thickness and posterior wall thickness to left ventricular mass are essentially the same in the cases studied. Cross-sectional area is thought to be useful for serial assessment of left ventricular hypertrophy because it incorporates into one index the two major determinants of mass measurable with echocardiography—wall thickness and the minor diameter of the left ventricle. However, we also estimated absolute left ventricular mass using echocardiographic posterior wall thickness, minor axis diameter and previously published regression equations.[17,18]

Comparison by linear regression of the 57 separate determinations of left ventricular mass (*LVM*), calculated according to cube function geometry, with the corresponding cross-sectional area (CSA) determinations, revealed that

$$LVM = 13.89\ (CSA) + 0.07 \quad [g], \tag{9}$$

with a correlation coefficient of 0.97, and the standard error of LVM on CSA of 26.3 g. Similarly, using a quadratic regression analysis of the relation between left ventricular internal diameter and angiographic left ventricular volume, reported by Ratshin et al.[18] and then translated into a mass equation by Devereux et al.,[17] we found that for the 57 echocardiograms in this study:

$$LVM = 12.81\ (CSA) - 67.99 \quad [g], \tag{10}$$

with a correlation coefficient of 0.97 and the standard error of LVM on CSA of 24.78 g. Thus, although we have chosen to present the cross-sectional area as a direct assessment of degree of left ventricular hypertrophy, estimations of absolute left ventricular mass can also readily be obtained using the preceding regression equations.

Assessment of the pattern of hypertrophy was obtained by relating the muscle cross-sectional area (index of mass) to the cavity cross-sectional area (index of volume); in eccentric hypertrophy the ratio of muscle to cavity cross-sectional area or mass to volume remains normal whereas in concentric hypertrophy these ratios are increased.[19] Linear regression of preoperative values for the mass/volume ratio (where mass and volume were calculated independently by equation 9 and equation 3, respectively) against the corresponding muscle cross-sectional area/cavity cross-sectional area ratio revealed a correlation coefficient of 0.99.

Paradoxical septal motion: This is an extremely common feature after aortic valve replacement.[20] To determine the effect of this wall motion abnormality on calculation of left ventricular performance from echocardiographic tracings, ejection fraction was also determined with first pass radionuclide angiography, a method that is unaffected by nonuniform left ventricular contraction or irregular geometry and that has been described and validated against contrast left ventriculography at our institution.[21,22] The radionuclide angiographic results were correlated with the concurrent echocardiographic determinations of ejection fraction, and a relatively poor correlation was noted ($r = 0.59$) (Fig. 3). However, this relation improved markedly ($r = 0.92$) when patients with paradoxical septal motion were excluded, and this finding strongly supports the notion that septal dyskinesia on echocardiography may not be adversely affecting global left ventricular shortening and is probably a movement related to loss of the normal external constraints imposed by the pericardial sac. Consequently, echocardiographic tracings that

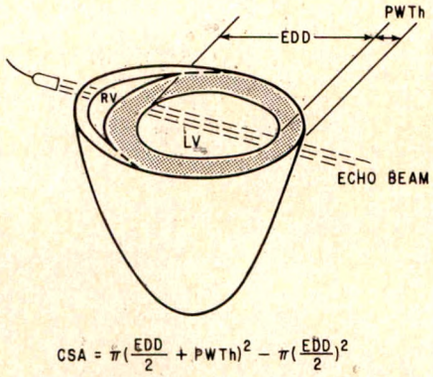

FIGURE 2. Method of calculating left ventricular (LV) wall cross-sectional area (CSA) (**stippled area**) as an index of left ventricular muscle mass from echocardiographic measurements of end-diastolic diameter (EDD) and posterior wall thickness (PWTh), assuming a uniform distribution of muscle mass around the entire left ventricular circumference. RV = right ventricle.

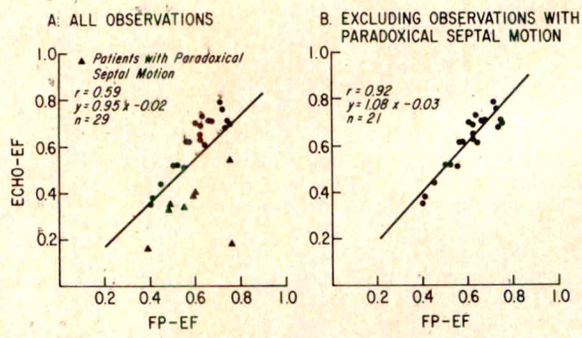

FIGURE 3. Correlation between ejection fraction determined concurrently with echocardiography (ECHO-EF) (**vertical axis**) and first pass radionuclide angiography (FP-EF) (**horizontal axis**). **A**, all observations regardless of presence or absence of septal dyskinesia; **B**, observations only in patients without septal dyskinesia. n = number of observations.

exhibited paradoxical septal motion were eliminated from the serial evaluation of ventricular performance, and no attempt was made to calculate from them the mean values for fractional shortening of the minor axis, ejection fraction or mean velocity of circumferential fiber shortening in either the early or late follow-up periods.

Analysis of data: To demonstrate trends within the serial noninvasive measurements, analysis of variance was performed on patients who had a complete set of four observations; patients with fewer than four observations were excluded from this evaluation. Also, in order to utilize the highest possible number of patients, the latest available postoperative observation was compared with control (preoperative) measurements using the paired t test.

Results

Hemodynamic and Angiographic Data

The left ventricular end-diastolic pressure was greater than 12 mm Hg in 11 of 15 patients [mean ± standard deviation 20 ± 10 mm Hg]. The preoperative left ventricular cineangiogram showed an enlarged left ventricular cavity and the supravalve aortogram demonstrated 3+ to 4+ aortic regurgitation in all patients. Four of the 16 patients (Cases 2, 5, 12 and 14) showed depression of left ventricular ejection phase indexes on left ventricular cineangiography, with an ejection fraction ranging below 0.48 (Table I).

Echocardiographic Measurements of Left Ventricle

End-diastolic dimension, posterior wall thickness and cross sectional area: *Analysis of variance:* In 10 patients with a complete set of four observations, the mean value for end-diastolic dimension before operation was 6.49 ± 0.84 cm (normal values in our laboratory are 4.7 ± 0.44 cm, range 4.31 to 5.32 cm). Immediately after operation there was a highly significant reduction in end-diastolic dimension to 5.10 ± 0.76 cm ($P < 10^{-5}$), representing a decrease of 21 percent from preoperative values. This dimension continued to decrease insignificantly at early (4.94 ± 0.70 cm) and at late follow-up (4.77 ± 0.57 cm); these latter values remained significantly different from preoperative values ($P < 10^{-5}$) and were well within normal range (Fig. 4, Table II).

The average preoperative posterior wall thickness was significantly increased (1.26 ± 0.13 cm, $P < 10^{-4}$) above standard normal values (0.92 ± 0.13 cm). Because left ventricular volume was considerably reduced while myocardial mass remained constant, immediately after operation there was a significant increase in posterior wall thickness (1.49 ± 0.18 cm, $P < 0.005$) by 18 percent as compared with preoperative values. At early follow-up, posterior wall thickness had decreased to preoperative values (1.19 ± 0.19 cm) and at late follow-up (1.13 ± 0.22 cm) was insignificantly smaller than preoperatively but was still significantly increased above normal ($P < 10^{-4}$) (Fig. 4, Table II).

The average preoperative cross-sectional area for the group was considerably larger (30.8 ± 5.7 cm^2) than the mean normal (16.1 ± 3.9 cm^2) and range (11.6 to 23.3 cm^2) ($P < 10^{-4}$). Despite considerable changes in end-diastolic dimension and posterior wall thickness at early follow-up, the cross-sectional area remained essentially unchanged and within the preoperative range (31.1 ± 6.3 cm^2). At early follow-up, it was reduced significantly (23.3 ± 6.2 cm^2, $P < 10^{-4}$) by 24 percent, with some further reduction noted at late follow-up (21.3 ± 6.3 cm^2, $P < 10^{-4}$). Despite a decrease of more than 30 percent in this index of muscle mass, at late follow-up it was still significantly elevated above normal values ($P < 0.005$) (Fig. 4, Table II).

TABLE II

Echocardiographic Measurements of End-Diastolic Dimension (EDD), Posterior Wall Thickness (PWTh), Left Ventricular Muscle Cross-Sectional Area (CSA) and Ratio of Wall (Muscle) Area/Cavity Area

Case	EDD				PWTh				CSA				Wall (muscle) Area/Cavity Area			
no.	Preop	F1	F2	F3	Preop	F1	F2	F3	Preop	F1	F2	F3	Preop	F1	F2	F3
1	7.75	5.19	5.22	4.76	1.45	1.93	1.48	1.42	42.1	43.1	31.2	27.5	0.89	2.04	1.46	1.55
2	7.08	5.32	4.16	4.32	1.18	1.45	1.04	0.93	30.5	30.8	17.0	17.6	0.78	1.39	1.25	1.05
3	7.30	4.60	4.98	4.76	1.10	1.63	1.27	1.05	29.0	31.8	24.9	19.2	0.69	1.92	1.28	1.08
4	6.50	6.19	6.33	6.17	1.34	1.49	1.25	1.32	33.0	35.9	29.7	31.2	0.99	1.19	0.95	1.04
5	6.73	6.06	5.22	4.86	1.39	1.37	1.23	1.04	35.7	32.0	25.0	19.3	1.00	1.11	1.16	1.04
6	6.24	5.84	5.55	5.00	1.44	1.57	1.47	1.49	34.7	36.6	32.5	30.3	1.14	1.36	1.34	1.55
7	5.50	4.14	4.46	4.77	1.20	1.46	0.92	0.94	25.4	25.8	15.6	16.8	1.06	1.91	1.00	0.94
8	5.06	4.06	4.25	4.36	1.20	1.37	1.12	0.92	23.6	23.4	18.9	15.3	1.17	1.81	1.33	1.02
9	5.82	4.90	5.08	4.07	1.12	1.28	0.95	0.95	24.4	24.8	18.0	15.0	0.92	1.32	0.89	1.15
10	6.98	4.67	4.16	4.63	1.16	1.38	1.23	1.27	29.8	26.2	20.8	23.6	0.78	1.53	1.53	1.40
11	6.71	5.41	4.19	...	1.11	1.26	0.94	...	28.3	26.4	18.1	...	0.77	1.15	0.86	...
12	6.60	...	...	4.14	1.32	...	...	1.34	33.0	...	...	23.0	0.96	...	...	1.71
13	6.13	4.98	4.38	...	1.39	1.50	1.25	...	32.7	30.5	22.2	...	1.11	1.57	1.47	...
14	6.84	...	4.87	4.61	1.38	...	1.12	0.90	35.6	...	21.1	15.6	1.03	...	1.13	0.93
15	6.22	4.50	5.11	...	1.47	1.87	1.30	...	35.5	37.4	26.2	...	1.21	2.35	1.28	...
16	6.85	...	4.26	4.15	1.28	...	1.33	1.03	32.7	...	23.4	16.9	0.89	...	1.64	1.24
no.	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Mean	6.49	5.10*	4.94*	4.77*	1.26	1.49*	1.19	1.13	30.8	31.1	23.3*	21.3*	0.94	1.56*	1.22	1.18
SD	0.84	0.76	0.70	0.57	0.13	0.18	0.19	0.22	5.7	6.3	6.2	6.3	0.16	0.33	0.22	0.23
SE	0.27	0.24	0.22	0.18	0.04	0.06	0.06	0.07	1.8	2.0	1.9	2.0	0.05	0.11	0.07	0.07

* Significantly different from preoperative value ($P < 0.01$).

F1 = at hospital discharge; F2 = 4 months after valve replacement; F3 = 15 months after valve replacement; Preop = preoperative; SD = standard deviation; SE = standard error.

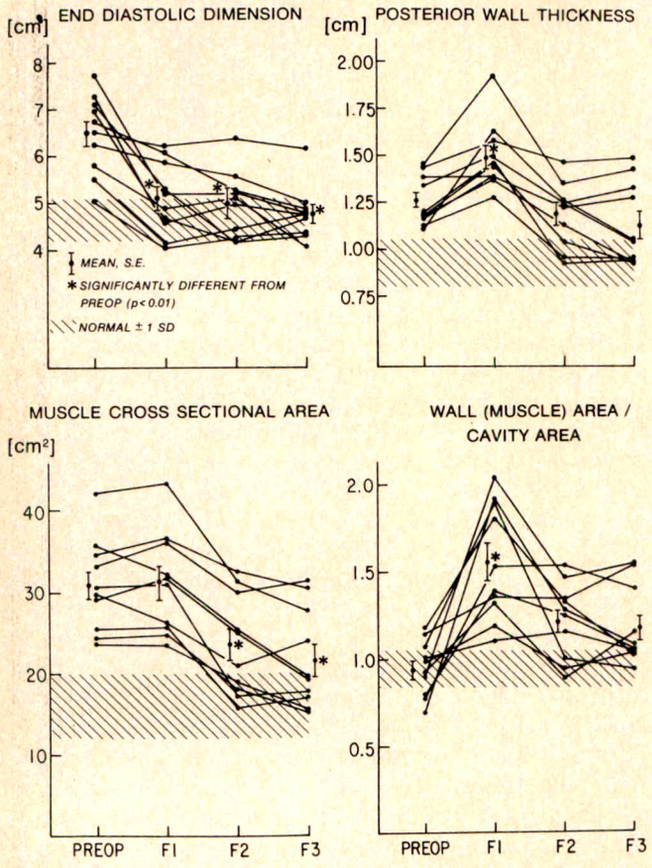

FIGURE 4. Serial changes of left ventricular hypertrophy and dimensions after aortic valve replacement (analysis of variance in patients with four observations over an average time span of 15 months). F1 = at hospital discharge; F2 = 4 months postoperative; F3 = 15 months postoperative; PREOP = preoperative; p = probability; SD = standard deviation; SE = standard error.

The preoperative ratio of muscle (ventricular wall) to cavity cross-sectional area (0.94 ± 0.16) was not different from normal (0.94 ± 0.11, range 0.81 − 1.16). Because of the marked reduction in end-diastolic diameter and increase in posterior wall thickness, immediately after operation there was a sharp increase in this ratio to 1.56 ± 0.33 (P <0.01); some regression was noted at early (1.22 ± 0.22) and at late follow-up (1.18 ± 0.23), and thereafter the average value was no longer significantly different from that of a group of normal subjects (Fig. 4, Table II).

Paired t *test:* All 16 patients had observations both before operation and at early or late follow-up. End-diastolic diameter decreased significantly from 6.52 ± 0.68 cm preoperatively to 4.64 ± 0.52 cm (P <0.01), posterior wall thickness from 1.28 ± 0.13 to 1.13 ± 0.20 cm (P <0.01) and cross-sectional area from 31.6 ± 4.8 to 21.1 ± 5.4 cm^2 (P <10^{-4}).

Left ventricular fractional shortening, ejection fraction, mean velocity of minor axis shortening: Preoperative findings are compared with the latest available follow-up data by paired t test in 13 patients; 3 patients were excluded because paradoxical septal motion persisted late after operation. There was no significant change in heart rate from the preoperative value of 69 ± 12 min^{-1} to the latest follow-up observation (66 ± 6 min^{-1}).

Preoperatively the mean values for fractional shortening (0.33 ± 0.09), ejection fraction (0.60 ± 0.14) and mean velocity of circumferential fiber shortening (1.05 ± 0.31 EDD sec^{-1}) were within the normal range. At late follow-up there was significant improvement in all three values (0.39 ± 0.07, P <0.05; 0.68 ± 0.10, P <0.05 and 1.26 ± 0.22, P <0.01 respectively) (Fig. 5, Table III). In two patients with paradoxical septal motion (Cases 14 and 15), the radionuclide ejection fraction showed normal values at late follow-up (Table III). Three patients (Cases 2, 12 and 14) with significant depression of left ventricular performance preoperatively manifested normal function indexes postoperatively. Ventricular function in one patient (Case 5) improved above preoperative values but remained abnormal (Table III). One patient (Case 6) manifested a low normal fractional shortening and ejection fraction before operation, and these values decreased slightly after operation.

Left ventricular regional myocardial performance: *Septal movement, posterior wall movement, normalized septal velocity and normalized posterior wall velocity: Analysis of variance:* On the basis of only the 10 patients with four observations, the mean value for septal movement preoperatively was 0.74 ± 0.32 cm; immediately after operation septal excursion became paradoxical in 7 of 10 patients with a mean value of −0.15 ± 0.52 cm (P <0.01). At early follow-up septal motion was still significantly reduced (0.25 ± 0.38 cm, P <0.05) from preoperative values; 2 of 10 patients had retained paradoxical septal motion. At late follow-up, septal movement continued to be less than the preoperative value (0.41 ± 0.29 cm), but the difference was no longer significant. Average posterior wall movement was normal preoperatively (1.55 ± 0.45 cm) and no significant change was noted immediately postoperatively (1.32 ± 0.25 cm) or at early (1.38 ± 0.24 cm) or late (1.39 ± 0.19 cm) follow-up (Fig. 6).

Immediately postoperatively there was a highly significant decrease of the average normalized septal velocity from 0.36 ± 0.16 to −0.15 ± 0.42 EDD sec^{-1} (P <0.01); however, at early follow-up, the average value had returned to 0.17 ± 0.25 EDD sec^{-1}, although two patients had paradoxical septal motion; the average value at late follow-up (0.28 ± 0.20 EDD sec^{-1}) was well within the preoperative range. Normalized posterior wall velocity increased from 0.79 ± 0.23 preoperatively to 1.06 ± 0.26 EDD sec^{-1} (P <0.01) immediately postoperatively, decreased slightly at early follow-up (0.96 ± 0.17 EDD sec^{-1}; P = not significant), and was significantly different from before operation at late follow-up (0.99 ± 0.12 EDD sec^{-1}; P <0.05) (Fig. 6).

Paired t *test:* Sixteen patients had observations before operation and at early or late follow-up. Septal movement decreased significantly from 0.74 ± 0.28 to 0.25 ± 0.37 cm (P <0.01) at late follow-up and posterior wall movement remained unchanged (preoperative 1.40 ± 0.44 cm; last follow-up 1.43 ± 0.24 cm); there was a significant decrease in normalized septal velocity (preoperative 0.37 ± 0.15; last follow-up 0.18 ± 0.26 EDD sec^{-1}; P <0.05), whereas normalized posterior wall

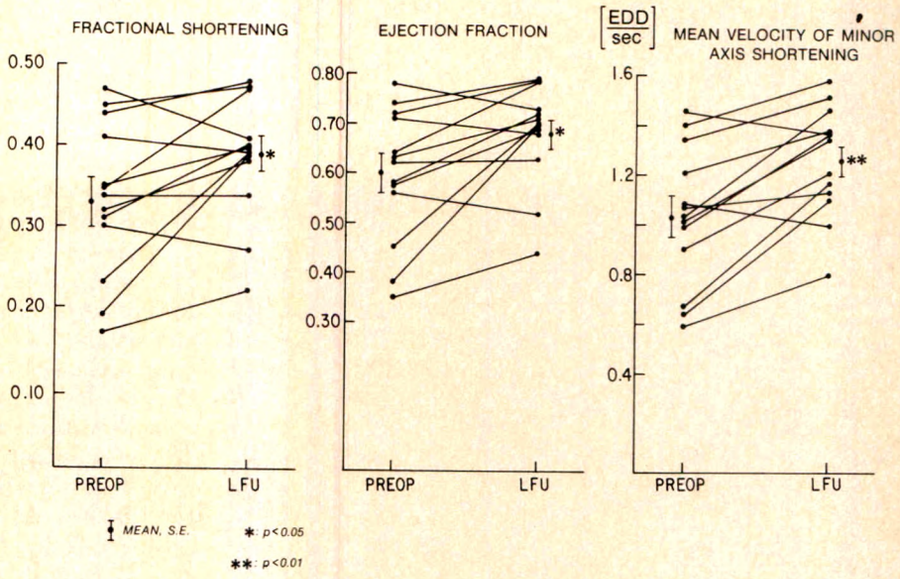

FIGURE 5. Echocardiographic indexes of left ventricular performance (fractional shortening, ejection fraction and mean velocity of circumferential shortening) before and late after aortic valve replacement (no. = 16, Student's *t* test). EDD = end-diastolic dimension; LFU = late follow-up; p = probability; PREOP = preoperative; S.E. = standard error.

velocity improved significantly from 0.68 ± 0.21 before operation to 1.02 ± 0.15 EDD sec^{-1} ($P < 0.001$) at late follow-up.

Discussion

Previous experimental animal studies have demonstrated enhanced pump performance of the left ventricle in response to chronic volume overload accomplished by chamber dilatation associated with maintenance of normal extent and speed of wall shortening per unit of circumference.[23,24] Myocardial hypertrophy occurs in concert with chamber dilatation and thereby may serve to normalize the force per unit cross-sectional area of myocardium. Despite these adaptations, left ventricular failure develops provided the volume overload is sufficiently severe and imposed over a long time period.[25–28] In man similar adaptive mechanisms appear to occur in response to the chronic left ventricular volume overload state caused by aortic regurgitation. However, the reversibility of myocardial hypertrophy and the temporal changes in left ventricular shortening characteristics once the aortic valve has been replaced have received relatively little study.

TABLE III

Echocardiographic and Radionuclide Data on Left Ventircular Performance Before and Late After Correction of Aortic Regurgitation

Case no.	HR		Δd/EDD		EF		Mean Vcf		RN-EF
	Preop	LFU	Preop	LFU	Preop	LFU	Preop	LFU	LFU
1	68	64	0.35	0.40	0.63	0.71	1.01	1.34	0.66
2	75	62	0.19	0.39	0.38	0.70	0.64	1.10	0.67
3	60	68	0.34	0.34	0.62	0.63	1.07	1.13	0.62
4	50	55	0.41	0.39	0.71	0.68	1.21	1.38	0.73
5	71	68	0.17	0.22	0.35	0.44	0.59	0.80	0.45
6	80	74	0.30	0.27	0.56	0.52	1.08	1.00	0.50
7	53	74	0.44	0.48	0.74	0.79	1.40	1.58	. . .
8	78	62	0.47	0.41	0.78	0.73	1.46	1.33	0.63
9	62	62	0.35	0.47	0.64	0.79	1.03	1.47	0.71
10	65	74	0.45	0.47	0.74	0.79	1.34	1.52	0.72
11	60	58	0.28	PSM	0.53	PSM	0.80	PSM	. . .
12	68	62	0.23	0.39	0.45	0.70	0.67	1.17	0.60
13	62	64	0.31	0.40	0.58	0.72	0.90	1.21	. . .
14	82	72	0.22	PSM	0.43	PSM	0.88	PSM	0.59
15	98	70	0.34	PSM	0.61	PSM	1.42	PSM	0.61
16	72	74	0.32	0.38	0.58	0.69	0.99	1.37	0.62
no.	16	16	13	13	13	13	13	13	13
Mean	69	66	0.33	0.39*	0.60	0.68*	1.05	1.26†	0.62
SD	12	6	0.09	0.07	0.14	0.10	0.31	0.22	0.08
SE	3	2	0.03	0.02	0.04	0.03	0.09	0.06	0.02

* Significantly different from preoperative value ($P < 0.05$).
† Significantly different from preoperative value ($P < 0.01$).
Δd/EDD = fractional shortening of minor axis; EF = echocardiographic ejection fraction; HR = heart rate (beats/min); LFU = latest available follow-up (average 9 months); no. = number of subjects; PSM = paradoxical septal motion; SD = standard deviation; SE = standard error; Vcf = velocity of minor axis shortening (end-diastolic dimension/sec).

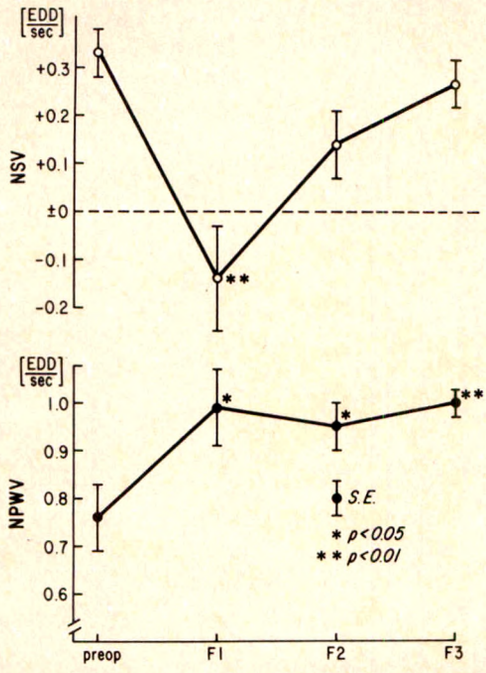

FIGURE 6. Serial changes in regional myocardial performance (septal velocity [NSV] and posterior wall velocity [NPWV]) normalized for end-diastolic dimension (10 patients with four observations, analysis of variance). EDD = end-diastolic dimension; other abbreviations as in Figure 4.

Regression of myocardial hypertrophy after aortic valve replacement: Previous reports on regression of myocardial hypertrophy, assessed with contrast angiography before and after correction of left ventricular overload, have been disparate. Baxley and Dodge[29] noted no significant change in left ventricular mass in patients observed for 4 to 14 months after successful correction of left ventricular volume overload; Kennedy et al.[6] reported significant but incomplete regression of left ventricular hypertrophy within 18 months after aortic valve replacement; Jamarkani et al.[30] reported in children a similar degree of regression of hypertrophy after closure of a ventricular septal defect. Experimental studies in animals have indicated that hypertrophy secondary to a volume overload is reversible once the inciting stimulus is removed; Papadimitriou et al.[31] noted considerable regression of left ventricular mass, as well as normalization of ultrastructural myofiber morphologic features, after correction of a volume overload state created in dogs by an aortocaval fistula. Interestingly, the time course of regression in these animals was closely parallel to that observed in our patients who had a significant regression of 31 percent of the original left ventricular cross-sectional area and 37 percent of the original left ventricular mass after valve replacement; thereafter, insignificant reduction was noted. In all of the human and experimental animal studies cited, regression appeared to be incomplete and the final estimates of left ventricular mass remained somewhat greater than normal values. Incomplete regression may be caused by the irreversibility of some myocardial elements, for example, fibrosis,[32,33] but another possible explanation in our patients is the mild to moderate pressure overload state associated with Hancock porcine heterografts in the aortic position.[14,15]

Mass-volume ratio after aortic valve replacement: Because wall thickness and minor axis chamber diameter are both readily obtained from the M mode echocardiogram, the ratio of muscle to cavity cross-sectional area was utilized in this study as an index of the mass/volume ratio. We thus evaluated the pattern of hypertrophy yet avoided making assumptions about left ventricular major axis dimensions. Moreover, we found that the ventricular wall area/cavity cross-sectional area ratio correlated with the mass/volume ratio (where volume and mass were calculated separately from previously published regression equations) with a correlation coefficient of 0.99. Before operation, although the absolute muscle cross-sectional area was found to be increased, the ratio of muscle to cavity area was normal, thereby documenting the well known presence of eccentric hypertrophy in patients with a volume overload.[34] Immediately after operation the ratio of muscle to cavity area increased significantly, from 0.94 to 1.56. Because the mass/volume ratio is recognized as an important determinant of systolic wall stress, and because peak systemic arterial pressure remained relatively unchanged, it can be concluded that a major immediate consequence of the operative intervention was a favorable reduction in left ventricular afterload. During the late follow-up period, a pattern of mild to moderate concentric hypertrophy persisted in six of the seven patients who continued to demonstrate an abnormal increase in the left ventricular cross-sectional area.

When calculating muscle and cavity cross-sectional areas from posterior wall thickness and end-diastolic diameter, we assumed a symmetric distribution of mass around a circumference of uniform diameter, which in some cases may be an oversimplication. However, the relative constancy of left ventricular cross-sectional area immediately postoperatively, when mass should remain unchanged despite the sudden reduction in end-diastolic dimensions, supports strongly the validity of this index as a measure of degree of hypertrophy (Fig. 4 and 5, Table II). Also, ultrasonic recordings of wall thickness and chamber diameter using implanted ultrasonic crystals in dogs subjected to pressure overload, led to similar conclusions.[35]

Postoperative indexes of contractile function: Most patients (11 of 16) in this analysis had normal extent and speed of minor diameter shortening at the time that aortic replacement was undertaken and they exhibited persistence of normal ejection phase indexes after operation; in addition, reduction in left ventricular chamber size occurred in all subjects. Moreover, the four patients with moderate preoperative impairment of left ventricular function (ejection fraction = 0.35 − 0.45, minor axis fractional shortening = 0.17 − 0.23, mean velocity of minor diameter shortening = 0.59 − 0.88 circumferences/sec) showed a definite tendency to improve; by 12 months or more after operation left ven-

tricular function was found to be normal in three of these patients (Cases 2, 12 and 14) and was considerably improved but remained mildly depressed in one patient (Case 5). Inexplicably, one subject (Case 6) demonstrated mild depression of left ventricular shortening postoperatively, even though the ejection phase indexes were all low normal before operation.

In contrast, Gault et al.[4] reported in 1970 detailed pre- and postoperative force-velocity-length analyses in patients with severe, chronic aortic regurgitation who underwent aortic valve replacement at our institution relatively late in the course of their disease; they found that in three of these patients with severely depressed myocardial contractility (minor axis fractional shortening 15 percent or less) preoperatively there was little, if any, improvement in myocardial shortening after operation (10 months or less) despite reduction in wall stress and alleviation of the patient's clinical symptoms. Also, these subjects manifested no regression of wall thickness or calculated cross-sectional area and demonstrated no reversal of an abnormal diastolic pressure-length relation. Although our Patients 5 and 6 had an abnormal extent of shortening postoperatively, both manifested a reduction in end-diastolic diameter, reduction in muscle cross-sectional area and an appropriate ratio of muscle to cavity area by the time of the late follow-up observations. Thus, none of the *preoperative* echocardiographic data were found to be predictive of postoperative depression of left ventricular function, persistence of a dilated left ventricular chamber or lack of regression of hypertrophy.

The fact that no patient in our group showed severe depression of left ventricular function comparable with that previously described in 1970 undoubtedly reflects less stringent clinical criteria for surgical intervention as operative techniques and mortality statistics improved over the last decade. Thus, we cannot precisely define what level of depressed left ventricular performance or what degree of dilatation and myocardial hypertrophy may constitute an irreversible state. However, we can conclude that uncomplicated correction of chronic severe aortic regurgitation, even when left ventricular function is moderately impaired, is associated with reduction in left ventricular size and normal or near normal values for extent and speed of wall shortening at an average of 15 months postoperatively.

Possible limitations of methodology: The reliability of pre- and postoperative assessment of left ventricular function with serial echocardiography and radionuclide angiography in chronic aortic regurgitation should also be considered. One potential source of error in measurement of minor axis chords using M mode ultrasound includes variation in recording technique and transducer placement.[36] To minimize this error, a record of transducer position for optimal minor axis visualization was made at the time of the preoperative study, and an effort to reproduce the identical position with the standard "landmarks" of the mitral valve leaflets was made at each subsequent visit. Linhart et al.[37] showed that sequential measurements in the same patient reflect dimensional changes with a high degree of reliability. Another conceivable error might arise from postoperative changes in chamber geometry. Formation of fibrous scar tissue adjacent to the heart after thoracotomy may distort left ventricular shape, change the major to minor axis ratio or alter the cardiac position and cause theoretically a nonrepresentative measurement of minor axis shortening on M mode echocardiography. However, the first pass radionuclide ejection fraction determinations do not depend on left ventricular geometry. As shown in Figure 4, the correlation between postoperative echocardiographic and radionuclide estimates of ejection fraction in patients without paradoxical septal motion was very high, and this finding also supports our contention that distortions of geometric shape are minor, if present, and do not invalidate the use of ultrasound for late postoperative estimates of average left ventricular shortening.

Implications: Serial application of M mode echocardiography to patients undergoing aortic valve replacement for chronic aortic regurgitation and left ventricular volume overload demonstrated significant regression of hypertrophy, a salutary change in the mass/volume ratio, as well as improvement in the extent and mean speed of myocardial shortening in the great majority of subjects studied over an average of 15 months after surgery. It is again noteworthy that all of our subjects had an appropriate pattern of hypertrophy and either normal or only moderate depression of myocardial shortening preoperatively, whereas similar serial observations on cardiac catheterization at this institution[1] in patients with severely reduced myocardial function demonstrated persistent, irreversibly depressed myocardial shortening up to 10 months postoperatively despite correction of the volume overload. Further serial studies in larger groups of patients should refine the preoperative mechanical characteristics that predict normal left ventricular and myocardial performance after surgery.

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Abbreviation of Systolic Time Intervals in Acute Mitral Regurgitation: Effect of Prosthetic Mitral Valve Replacement

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Systolic time intervals were measured in 26 patients with mitral regurgitation (acute in 14 and chronic in 12). In 13 of these patients (7 with acute and 6 with chronic mitral regurgitation) systolic time intervals were also measured after mitral valve replacement. Total electromechanical systole corrected for heart rate (Q-S_2I) was of much shorter duration in the group with acute mitral regurgitation (472 ± 9 msec [mean ± standard error of the mean]) than in the group with chronic mitral regurgitation (516 ± 4.6 msec, $P < 0.01$). Before operation, the ratio of the preejection period (PEP) to left ventricular ejection time (LVET) and the angiographic ejection fraction did not differ in the groups with acute and chronic mitral regurgitation. The correlation between the PEP/LVET ratio and ejection fraction was $r = -0.84$, $P < 0.01$. Two weeks after operation, the PEP/LVET ratio increased in all patients, but the increase was greater in those with lower preoperative values for this ratio. The mechanism of the early postoperative increase in the PEP/LVET ratio is not clear, but serial studies performed over 6 months showed a return toward the preoperative value. It is concluded that preoperative systolic time intervals are useful for assessing left ventricular performance in all types of mitral regurgitation, but are especially useful for distinguishing between the acute and chronic varieties.

In spite of modern diagnostic techniques, the preoperative evaluation of left ventricular performance in mitral regurgitation remains a significant problem.[1–5] In part, this is because mitral regurgitation of various degrees is a common result of primary left ventricular disease. Although the amount of regurgitation in patients with such disease is not often great, it can be equal to the forward stroke volume.[6–9] In addition, there appears to be a substantial hemodynamic difference between acute and chronic mitral regurgitation.[8,10–16]

Systolic time intervals have been used as a quantitative noninvasive technique for evaluating left ventricular performance.[17–19] In this study we attempted to clarify the usefulness of these intervals in assessing left ventricular function in patients with acute and chronic mitral regurgitation. We hypothesized that patients with significant left ventricular disease in association with mitral regurgitation could be identified with these intervals. Although this proved to be true, two unexpected phenomena were present. First, patients with acute mitral regurgitation exhibited a marked abbreviation of the primary systolic time intervals. Second, the preejection period/left ventricular ejection time (PEP/LVET) ratio increased significantly in the early postoperative period in nearly all patients. Consequently we also studied a group of patients

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with isolated mitral stenosis before and after mitral valve replacement.

Methods

Patients: Twenty-six patients with mitral regurgitation (acute in 14, chronic in 12) and 15 patients with mitral stenosis were studied. The 14 patients with acute mitral regurgitation had ruptured chordae tendineae due either to myxomatous degeneration (8 patients) or to myocardial infarction (6 patients). The 12 patients with chronic mitral regurgitation had rheumatic heart disease with predominant mitral regurgitation and trivial or absent mitral stenosis. Patients with significant involvement of other valves were excluded.

The administration of medications remained constant throughout the study. Seven patients with acute mitral regurgitation were receiving digitalis, as were 11 patients with chronic mitral regurgitation. All patients with postoperative sepsis, myocardial infarction or valve malfunction were excluded from the study.

Statistical analysis was performed using Student's *t* test.

Systolic time intervals: These measurements were obtained in all patients the day before cardiac catheterization, as previously described.[17,19] The ratio of the preejection period (PEP) to left ventricular ejection time (LVET) was used as the primary measure of left ventricular performance.[17–19] To avoid variations in the measurement of the ejection fraction and PEP/LVET ratio when atrial fibrillation was present, we excluded beats with a preceding R-R interval shorter than 800 msec.[20]

Left and right heart catheterization: These procedures were performed preoperatively in all patients. Quantitative left ventricular cineangiograms were obtained in the 30 degree right anterior oblique position. Left ventricular volumes were calculated using the area-length method.[21] Selective coronary cineangiography was performed in all patients with acute mitral regurgitation. Coronary artery disease with myocardial infarction was found in six.

Surgical follow-up: Thirteen of the 26 patients with mitral regurgitation (7 acute, 6 chronic) and all patients with mitral stenosis were also studied before and 2 weeks after mitral valve replacement with systolic time intervals, a RISA cardiac output, and a chest X-ray film for quantitation of heart size.[22,23] In addition, eight patients with mitral regurgitation and four patients with mitral stenosis were studied 6 months after surgery.

Results

Preoperative values: The clinical and hemodynamic data of patients with mitral regurgitation are shown in Tables I and II. The intracardiac pressures and the ejection fraction were similar in the groups with acute and chronic regurgitation. However, the patients with acute regurgitation had a larger left ventricular end-diastolic volume and a lower value for aortic diastolic pressure.

TABLE I

Clinical Data in Patients With Acute and Chronic Mitral Regurgitation

	Cases (no.)	Age (yr)	Sex	NSR	AF	Duration of Symptoms
Acute	14	50.1 ± 3.8*	7F, 7M	8	6	7.5 ± 1.4 mo
Chronic	12	44 ± 3.0	7F, 5M	1	11	5.6 ± 1.5 yr
P		NS	NS	0.02	0.02	<0.001

* 1 standard error of the mean

AF = atrial filbrillation; NS = not significant; NSR = normal sinus rhythm; *P* = probability.

Before operation, all of the systolic time intervals were significantly shorter in patients with acute than in those with chronic mitral regurgitation (Fig. 1). The individual values for total electromechanical systole corrected for heart rate ($Q\text{-}S_2I$) for the two groups are shown in Figure 2.

The preejection period/left ventricular ejection time (PEP/LVET) ratio was not significantly different in the two groups, and there was an excellent correlation between the PEP/LVET ratio and left ventricular ejection fraction (Fig. 3).

Early postoperative values: The preoperative and postoperative systolic time intervals in 13 patients with mitral regurgitation are indicated in Table III. The PEP/LVET ratio 2 weeks after operation increased significantly in both groups. There was a good positive correlation between the increase in the PEP/LVET ratio 2 weeks after operation and the preoperative left ventricular ejection fraction ($r = 0.78$, $P < 0.001$). Thus, patients with a higher preoperative ejection fraction had a greater increase in the PEP/LVET ratio after operation.

TABLE II

Hemodynamic Data in Patients With Acute and Chronic Mitral Regurgitation

	Cases (no.)	Pressures (mm Hg) SAP	DAP	LVEDP	PCW Mean	PCW *V* Wave	SPAP	DPAP	LVEDVI	CI	EF
Acute	14	122 ± 5*	65 ± 5	16 ± 2	20 ± 3	43 ± 6	50 ± 6	21 ± 3	155 ± 10	2.6 ± 0.3	59 ± 4
Chronic	12	131 ± 8	83 ± 5	14 ± 1	24 ± 3	41 ± 4	47 ± 6	22 ± 3	112 ± 10	2.2 ± 0.3	57 ± 4
P		NS	<0.02	NS	NS	NS	NS	NS	<0.02	NS	NS

* 1 standard error of the mean.

CI = cardiac index (liters/min per m^2); DAP = diastolic aortic pressure; DPAP = diastolic pulmonary arterial pressure; EF = ejection fraction (percent); LVEDP = left ventricular end-diastolic pressure; LVEDVI = left ventricular end-diastolic volume index (ml/m^2); NS = not significant; *P* = probability; PCW = pulmonary capillary wedge pressure; SAP = systolic aortic pressure; SPAP = systolic pulmonary arterial pressure.

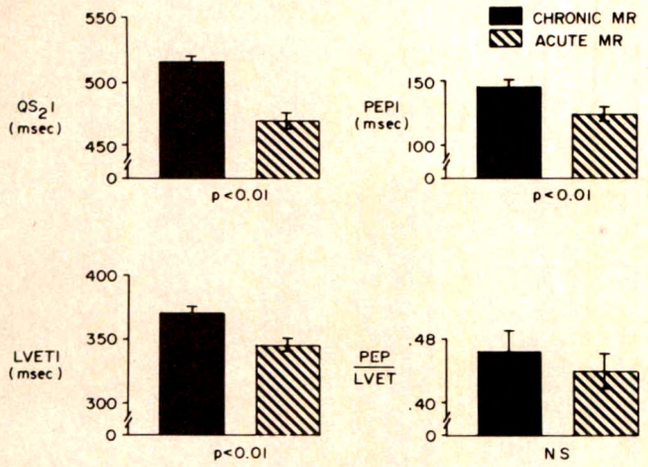

FIGURE 1. Systolic time intervals (mean ± 1 standard error of the mean) in patients with acute and chronic mitral regurgitation (MR). All the systolic time intervals, including total electromechanical systole ($Q\text{-}S_2I$), left ventricular ejection time (LVETI) and preejection period (PEPI), were significantly shorter in patients with acute mitral regurgitation. PEP/LVET ratio was the same in both groups. p = probability.

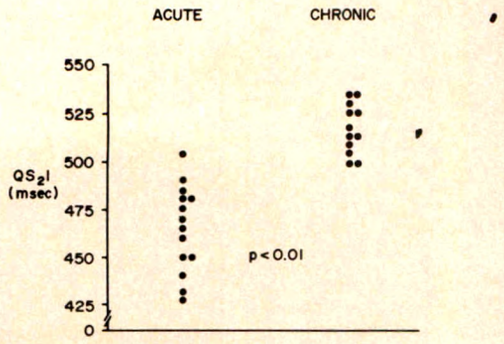

FIGURE 2. Individual $Q\text{-}S_2I$ values for patients with acute and chronic mitral regurgitation. Note the nearly complete separation between the two groups. p = probability.

In the patients with acute mitral regurgitation the $Q\text{-}S_2I$ interval and the preejection period index were significantly prolonged after operation whereas the left ventricular ejection time index did not change significantly. In patients with chronic regurgitation none of these three indexes changed significantly. The cardiac index increased significantly after operation in all 13 patients (3.4 ± 0.02 versus 2.4 ± 0.3 liters/min per m^2, $P < 0.01$). There were no significant changes in blood pressure 2 weeks after operation from that measured before operation.

The PEP/LVET ratio was unchanged 2 weeks after operation in the 15 patients who had mitral valve replacement for mitral stenosis (preoperative 0.42 ± 0.02, postoperative ratio 0.40 ± 0.02). At the same time, the cardiac index increased from 2.4 ± 0.06 to 3.3 ± 0.01 liters/min per m^2. The preoperative left ventricular end-diastolic volume in the patients with mitral stenosis was normal (63 ± 7 ml/m^2).

Late postoperative values: Six months after surgery for mitral regurgitation, the PEP/LVET ratio was lower than the early postoperative values, but still above the preoperative value (Fig. 4). The improvement in the PEP/LVET ratio was accompanied by a decrease in the frontal heart area measured from the chest X-ray film.

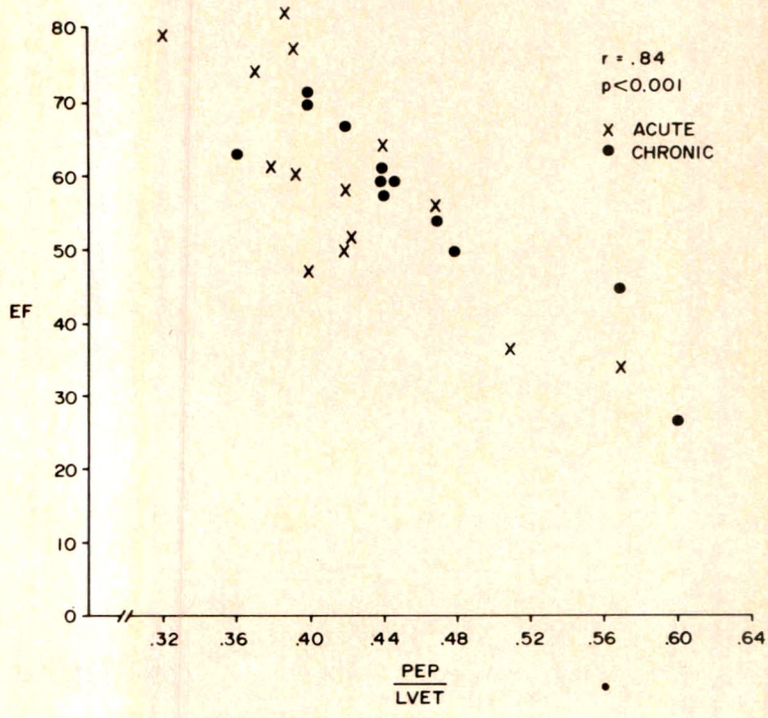

FIGURE 3. Relation between left ventricular ejection fraction (EF) and PEP/LVET ratio measured angiographically before operation. An excellent correlation is present. p = probability; r = correlation coefficient.

TABLE III

Pre- and Postoperative Systolic Time Intervals (mean ± 1 standard error of the mean) in 13 Patients With Acute (no. = 7) and Chronic (no. = 6) Mitral Regurgitation

	Q-S_2I (msec)		LVETI (msec)		PEPI (msec)		PEP/LVET	
	Acute	Chronic	Acute	Chronic	Acute	Chronic	Acute	Chronic
Preop	475 ± 8	515 ± 10*	350 ± 8	372 ± 7*	125 ± 10	143 ± 8*	0.43 ± 0.02	0.47 ± 0.02
Postop	492 ± 7	510 ± 9*	343 ± 7	360 ± 10*	149 ± 4	150 ± 6	0.59 ± 0.02	0.56 ± 0.02
$P^{\dagger}$	<0.05	NS	NS	NS	<0.01	NS	<0.001	<0.001

* Significant difference between values in patients with mitral regurgitation acute and chronic ($P < 0.05$).
† Difference between pre- and postoperative values.
LVETI = left ventricular ejection time index; NS = not significant; PEPI = preejection period index; PEP/LVET = preejection period/left ventricular ejection time; Preop = preoperatively; Postop = postoperatively.

In patients with mitral stenosis, no change in the PEP/LVET ratio was observed 6 months after operation (0.40 ± 0.02 two weeks postoperatively, 0.41 ± 0.02 six months postoperatively).

Discussion

Ventricular performance in mitral regurgitation: Hemodynamic performance in patients with mitral regurgitation tends to be preserved because of an increase in end-diastolic volume and a decrease in afterload.[3,6] In experimental acute mitral regurgitation, the dilated left ventricle contracts to a normal end-systolic volume leading to an increased ejection fraction.[24] Thus, a "normal" ejection fraction in the presence of acute mitral regurgitation may imply that some left ventricular dysfunction is present.[1–3]

A previous study[25] in a smaller series of patients with mitral regurgitation had shown that the preejection period/left ventricular ejection time (PEP/LVET) ratio is a valid measure of left ventricular performance. This was confirmed in our study. Left ventricular function was not significantly different in our patients with acute and chronic mitral regurgitation, as observed by other investigators.[14,15] However, patients with acute mitral regurgitation had a greater variability in left ventricular performance, largely because the acute regurgitation was a result of myocardial infarction in nearly half of the patients.

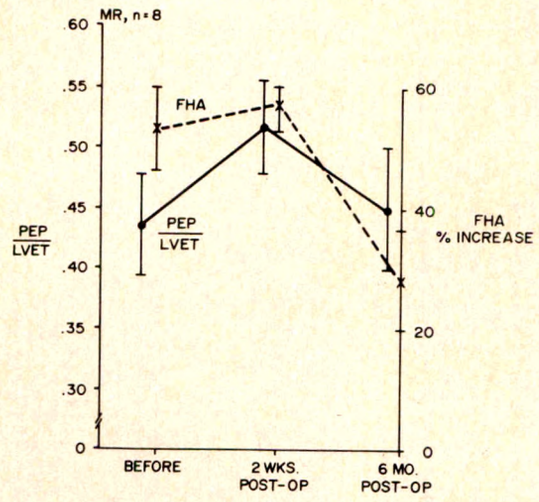

FIGURE 4. Changes in preejection period/left ventricular ejection time (PEP/LVET) ratio and frontal heart area (FHA) measured from a standard chest X-ray film after mitral valve replacement. The decrease in the PEP/LVET ratio 6 months postoperatively was associated with a decrease in frontal heart area. POST-OP = postoperatively.

Acute versus chronic mitral regurgitation: Although preoperative hemodynamics and left ventricular function, as judged from the ejection fraction and PEP/LVET ratio, were not different in the patients with acute and chronic mitral regurgitation, the duration of the systolic time intervals differed substantially in the two groups. Acute mitral regurgitation was associated with a marked shortening of all three primary systolic time intervals, and the separation between the two groups was nearly complete for total electromechanical systole corrected for heart rate (Q-S_2I).

Previous studies have suggested that there is a significant hemodynamic difference between acute and chronic mitral regurgitation. It has been hypothesized that in acute mitral regurgitation, considerable regurgitation occurs during isovolumic systole.[7] This could account for shortening of the systolic time intervals due to juxtaposition of the preejection period and left ventricular ejection time. Chronic mitral regurgitation usually is the result of rheumatic valve disease in which the mitral valve is thickened and restricted. In contrast, in acute mitral regurgitation the mitral valve leaflet or leaflets are flail. This could result in a greater degree of regurgitation before aortic valve opening in patients with acute mitral regurgitation.

Hemodynamic studies[26] have demonstrated restriction of cardiac volume by the pericardium in acute mitral regurgitation, and patients with constrictive pericarditis have been shown to have short systolic time intervals.[27] However, the hemodynamic data do not suggest that restrictive physiology played a major role in our patients with acute mitral regurgitation. Finally, increased adrenergic activity could shorten the Q-S_2I interval. We do not have urinary catecholamine data to establish this point, but it is of interest that the Q-S_2I interval lengthened after mitral valve replacement.

Other investigators[9,25] have noted that systolic time intervals are not short in chronic mitral regurgitation. If, as in our study, one excludes beats with short preceding R-R intervals when atrial fibrillation is present,

the average Q-S_2 interval will be shorter.[23] The majority of our patients with chronic mitral regurgitation had atrial fibrillation whereas this was not true in the group with acute mitral regurgitation. Furthermore, digitalis would tend to shorten the Q-S_2I interval and most of our patients with chronic regurgitations were receiving this drug compared with only 50 percent of those with acute regurgitation. In view of these considerations, the separation of the two groups is all the more remarkable.

Short systolic time intervals in diagnosis of acute mitral regurgitation: Although our data do not allow definition of the mechanism of the short systolic time intervals in acute mitral regurgitation, the observation remains clinically useful for identifying this group of patients. The diagnosis of acute mitral regurgitation is often difficult even with echocardiography and left ventricular cineangiography. Indeed, in our laboratories the finding of a greatly abbreviated Q-S_2I interval in a patient with the appropriate clinical findings of mitral regurgitation has been virtually diagnostic of acute mitral regurgitation.

Cause of increased PEP/LVET postoperatively: The early postoperative increase in the PEP/LVET ratio is not readily explained. All patients had clinical improvement and the mean cardiac index had returned to normal. The increase was found both in patients with acute and in patients with chronic mitral regurgitation. Among possible explanations are intraoperative myocardial injury, masked preoperative left ventricular dysfunction, decreased postoperative adrenergic tone, increased afterload and decreased preload. We deliberately excluded patients with postoperative myocardial injury.[28] The increase in the PEP/LVET ratio was most striking in patients with good preoperative left ventricular function. This finding suggests that masked left ventricular dysfunction is not the explanation. The short Q-S_2I values in all postoperative patients (as well as data from other studies[28]) indicate that the increase is not due to diminished adrenergic tone in the early postoperative period. An increase in afterload is a definite possibility because of the elimination of ejection in the low pressure left atrial chamber. However, our data do not allow quantitation of this possibility.

A decrease in preload remains the most attractive hypothesis. This could result from persistence of the increased left ventricular end-diastolic volume caused by the mitral regurgitation. We have noted such early postoperative increases in the PEP/LVET ratio (in the absence of myocardial injury) only in patients with volume overload.* The same phenomenon has also been noted in other studies in which left ventricular performance was measured without use of systolic time intervals.[29,30] Our patients with mitral stenosis and normal preoperative left ventricular volumes did not exhibit this phenomenon.

By 6 months, when heart size had considerably decreased, the PEP/LVET ratio had returned toward but was still above the preoperative value. Regardless of the explanation for this unusual finding, it appears to be benign. The implication appears to be that evaluation of left ventricular performance after valve replacement for mitral regurgitation should be postponed until at least 6 months after operation.

Acknowledgment

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* The same phenomenon was noted in five patients with aortic regurgitation in whom the systolic time intervals were measured before and 2 weeks and 6 months after aortic valve replacement. In these patients the PEP/LVET ratio 2 weeks after operation was 0.61 ± 0.03 and the frontal heart area 52 ± 6 percent above normal. Six months later the PEP/LVET ratio and frontal heart area decreased significantly (0.47 ± 0.02 and 21 ± 5 percent, respectively, $P < 0.01$).

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Effects of Coronary Bypass Grafting on Resting Left Ventricular Contraction in Patients Studied 1 to 2 Years After Operation

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Left ventricular contraction was evaluated with angiography in 51 patients 1 to 2 years after coronary arterial bypass surgery. The left ventricle was classified into five segments, and segmental ventricular wall motion was analyzed with subjective and objective methods. With subjective analysis, 25 percent of asynergic segments showed improvement, 72 percent no change and 3 percent deterioration in contraction. There was a 5 percent incidence rate of new wall motion abnormalities in segments that were judged normal from the preoperative ventriculogram. Objective analysis revealed significant improvement in contraction of asynergic segments in each of the five left ventricular segments analyzed. Thus, 1 to 2 years after coronary bypass surgery, there was a significant reduction in left ventricular segmental wall motion abnormalities, and the incidence of deterioration in contraction was small.

The influence of successful coronary arterial bypass surgery on resting left ventricular function remains controversial. Theoretically, contraction of abnormal left ventricular segments that are acutely or chronically ischemic should improve after successful revascularization, and segments that are fibrosed or infarcted should not change. Prior studies have yielded variable results in terms of improvement in left ventricular asynergy or other indexes of left ventricular function at rest.[1–8] We studied the effects of coronary bypass surgery on resting left ventricular function in 51 patients who consented to coronary arterial and graft angiography, as well as ventriculography, 1 to 2 years after operation.

Methods

Patients: The 51 patients studied were part of a consecutive series of 106 patients undergoing coronary arterial bypass surgery between January 1974 and November 1975. Indications for operation were the presence of symptoms of myocardial ischemia or insufficiency, unrelieved by medical management, and significant narrowing (50 percent or greater narrowing of luminal diameter) of one or more major coronary arteries. Unstable angina was present in 54 patients and congestive heart failure in 8. Four patients had evolving acute myocardial infarction at the time of operation. Intraaortic balloon pumping was used preoperatively to provide support for two patients with cardiogenic shock and for seven patients who required control of ischemic symptoms. During operation systemic hypothermia to 28° C was induced with a heat exchanger, and topical myocardial cooling was also used for myocardial preservation. There were four operative deaths (3.8 percent) and one death occurring early (less than 30 days) during the hospital stay.

All patients were asked to undergo coronary angiography 1 to 2 years after operation. Sixty-three patients consented to the study. Twelve patients were

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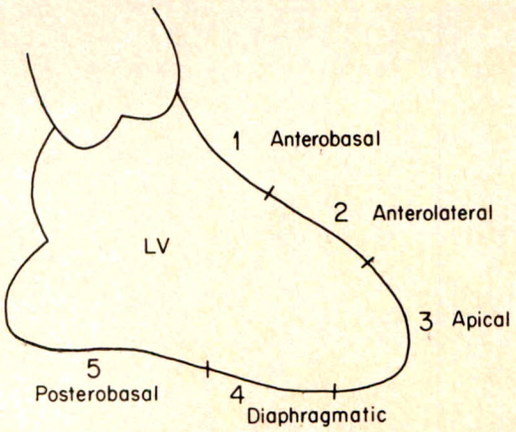

FIGURE 1. Left ventricular segments used in the subjective analysis of left ventricular wall motion before and after coronary bypass surgery.

excluded because their angiographic studies were judged technically unsatisfactory for the ventricular wall motion analysis central to this project. The remaining 51 patients undergoing late coronary angiography with satisfactory pre- and postoperative ventriculograms 1 to 2 years (average 17 months) after operation formed the study group.

Twenty of the 51 patients had unstable angina, as defined by a crescendo anginal pattern with pain occurring at rest, and 31 had stable angina pectoris. Five patients had significant left main coronary arterial stenosis, and 20 patients had three vessel, 20 two vessel and 11 single vessel coronary artery disease. On the basis of Q waves in the electrocardiogram, 19 patients had a previous acute myocardial infarction. Three patients had a perioperative infarction, and one patient an acute myocardial infarction in the year after operation.

Coronary angiography, graft angiography and left ventriculography: These procedures were performed using the Judkins technique. There were no complications in the preoperative or late postoperative studies. Left ventricular end-diastolic pressure, heart rate and systemic arterial pressure were measured before injection of contrast medium. Ventriculography, performed before coronary and graft angiography, consisted of a single plane 30° right anterior oblique view. Forty to 55 cc of Renografin-76® was injected at 13 to 15 cc/sec to opacify the left ventricle. Ejection fraction was determined using the area-length method.

The ventricle was classified into five segments for evaluation of regional wall motion: anterobasal, anterolateral, apical, inferior and posterobasal (Fig. 1). On the basis of the preoperative left ventriculogram two independent observers classified each segment subjectively as normal, hypokinetic, akinetic or dyskinetic. Differences were resolved by consensus. They also evaluated subjectively changes in regional wall motion in the postoperative ventriculograms. The pre- or postoperative status of the ventriculograms could not be hidden from the observers because of the many clues, such as sternal wires or graft clips, indicating that a given ventriculogram was a postoperative study.

Objective analysis of regional wall motion: Because the subjective method uses only three grades of left ventricular dysfunction and may not detect subtle changes in contraction, objective analysis was also performed. The end-diastolic (largest frame) and end-systolic (smallest frame) images were traced using the ribs and diaphragms as reference points. The longest axis of the end-diastolic left ventricle (from the midpoint of the aortic valve to the apex) was crossed on the tracing by four equidistant perpendicular lines, giving eight hemiaxes (Fig. 2). Percent hemiaxis and apex-to-base shortening were computed. The left ventricle was classified into the same five segments used for subjective analysis.

Motion of the anterobasal, anterolateral, inferior and posterobasal segments was defined by the average percent

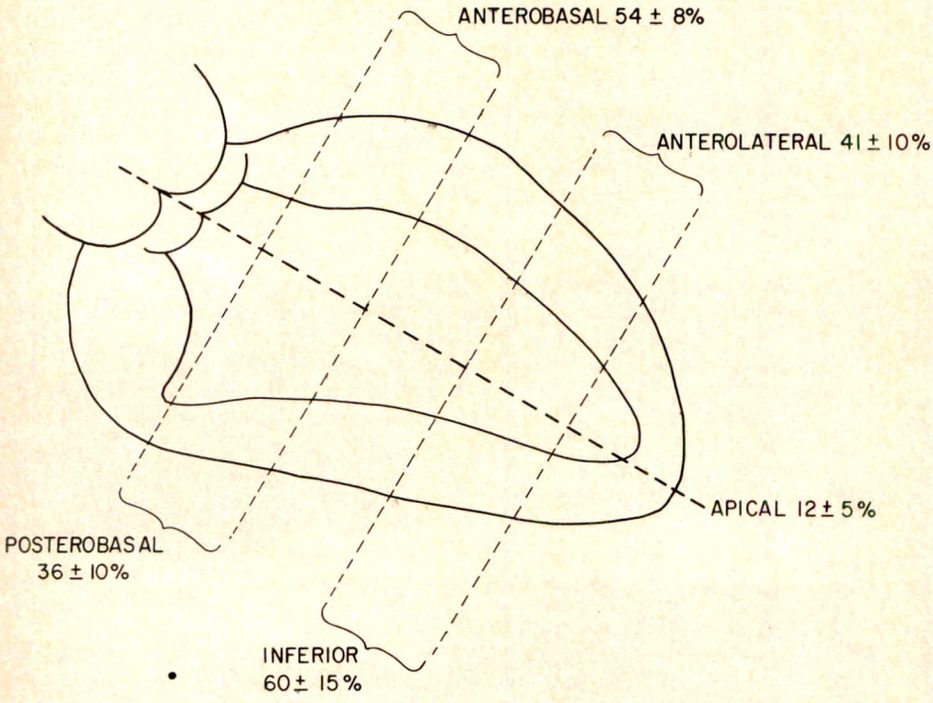

FIGURE 2. Left ventricular hemiaxes used in the objective analysis of wall motion before and after coronary bypass surgery. Normal values for percent of hemiaxis shortening are shown (mean ± 1 standard deviation).

shortening of two hemiaxes per segment (Fig. 2). The motion of the apical segment was defined by percent apex-to-base shortening. Percent segmental wall motion was calculated from the pre- and postoperative ventriculograms. Asynergy was defined as percent segment shortening less than 2 standard deviations from mean normal values.

Normal values for percent shortening for each segment were obtained from 20 patients with normal coronary angiograms and left ventricular end-diastolic pressure who underwent cardiac catheterization for the evaluation of chest pain. None of these patients had valve lesions, cardiomyopathy or abnormal septal motion. The normal values for each segment are shown in Figure 2.

The objective analysis of regional wall motion was evaluated by one investigator. Ventriculograms from 20 study patients were randomly selected and traced a second time and ejection fraction and percent segment shortening determined. The mean percent difference in the ejection fraction between the first and second tracing was 1 ± 4 percent (± 1 standard deviation) The mean percent difference in measurement of hemiaxes was 2 ± 8 percent.

Correlation of coronary disease, graft patency and wall motion: In the preoperative study the vascular supply to each of the left ventricular segments was noted, and the major arteries were graded for percent diameter narrowing. A significant stenosis was defined as a 50 percent reduction in luminal diameter in any one view. The postoperative coronary angiograms and graft angiograms were studied for changes in the native circulation and for graft patency. Progression of disease in native vessels, as judged from the late postoperative angiogram, was defined as development of 50 percent or greater reduction in luminal diameter or new total occlusion. Segmental wall motion was correlated with graft patency and with electrocardiographic Q waves.

Statistical analysis was performed using an analysis of variance and Student's *t* test for paired values where appropriate.

Results

In the 51 patients whose ventriculograms were analyzed, a total of 95 vein grafts and 4 left internal mammary to left anterior descending arterial grafts were performed (approximately 2 grafts per patient); the late graft patency rate was 95 percent. Two vein grafts showed significant stenosis, one of 50 percent and one of 70 percent reduction in diameter. Three patients had a perioperative myocardial infarction (as judged from new Q waves in the electrocardiogram), and one patient had an infarction in the year after operation. There were no late deaths in the study population over the 1 to 2 year period that encompassed operation and the late angiographic study. There was a very small incidence of progression of disease in native vessels that were not bypassed (one vessel) and in the distal vessels of arteries that were bypassed (two vessels).

Subjective analysis of wall motion: Of the total of 255 left ventricular segments 179 (70 percent) manifested normal contraction in the preoperative ventriculogram. Of these, 170 (95 percent) remained normal whereas 9 (5 percent) were judged asynergic postoperatively. Six segments that continued to show normal contraction postoperatively were supplied by the five vein grafts that had occluded after operation. None of the nine segments that had become asynergic were supplied by an occluded or significantly stenotic vein graft. In six of the nine segments that became asynergic, there was a possible cause of the deterioration in contraction: perioperative myocardial infarction (three segments), myocardial infarction in the interval between operation and the follow-up study (one segment) and supply by arteries that were significantly stenotic, but that had been judged at operation to be not satisfactory for placement of a bypass graft (two segments). In the remaining three segments, no reason for the deterioration in contraction was apparent.

TABLE I

Postoperative Status of 76 Segments Judged Asynergic on Preoperative Subjective Evaluation

Preoperative Degree of Asynergy	Postoperative Status			
	Unchanged	Improved	Worse	Total
Hypokinetic	32	12	2	46
Akinetic	20	5	0	25
Dyskinetic	3	2	0	5
Total	55 (72%)	19 (25%)	2(3%)	76 (100%)

Subjectively, 76 (30 percent) of the 255 left ventricular segments were judged asynergic in the preoperative study. Thirty-four of the 51 patients had at least one asynergic zone. Forty-six of the asynergic segments were hypokinetic, 25 akinetic and 5 dyskinetic. Fifty-five (72 percent) of the asynergic segments were not changed after operation, whereas 19 (25 percent) showed improvement and 3 percent deterioration in contraction (Table I). Although most of the segments with improved contraction were hypokinetic, some were akinetic or dyskinetic.

Twenty-three (40 percent) of the 55 asynergic segments that did not manifest improved contraction after operation were a site of preoperative myocardial infarction as revealed by electrocardiographic Q waves, but this was also true of 10 (53 percent) of the asynergic segments with improved contraction (Table II). Only one graft supplying an asynergic segment had occluded, and that segment was unchanged in the postoperative

TABLE II

Factors Affecting Segmental Contraction and Postoperative Status of Segments Studied

	Postoperative Status		
	Unchanged (55 segments)	Improved (19 segments)	Worse (2 segments)
Myocardial infarction			
Preoperative	23	10	0
Perioperative	0	0	1
Postoperative	0	0	0
Graft closure	1	0	0
Diseased artery not bypassed	10	3	0
No significant coronary artery disease	2	0	0

study. The two vein grafts that showed significant stenosis in the postoperative study supplied left ventricular segments that had been asynergic preoperatively. One segment showed no change, the other improved contraction postoperatively. Sixteen of the 19 left ventricular segments with improved contraction postoperatively were supplied by patent bypass grafts. For unknown reasons, 3 of these 19 segments were supplied by significantly diseased arteries, which were judged at operation to be unsuitable for bypass. One of the two hypokinetic segments judged worse postoperatively was the site of a perioperative myocardial infarction. This was an anteroseptal infarction that developed with Q waves in precordial leads V_2 and V_3 in association with deterioration in contraction of the anterolateral wall. However, the patient in this case had a patent graft to the anterior descending branch of the left artery.

Objective analysis of wall motion (Table III): In the objective study 194 (76 percent) of the 255 segments were normal in preoperatively, and normally contracting segments showed no statistically significant change in motion after operation, with the exception of a small decrease in mean percent shortening in the anterobasal segment from 52 ± 12 to 47 ± 15 percent ($P < 0.05$). Although statistically significant, the 5 percent decrease in the anterobasal segment may be attributed to the error of the method of tracing hemiaxes. The mean difference in duplicate hemiaxes determinations was 2 ± 8 percent (± 1 standard deviation). Significant improvement was observed postoperatively in asynergic segments. Twelve of the 194 normal segments (7 percent) showed new asynergy after operation. Asynergy increased by more than 10 percent in only one asynergic segment.

Comparison of subjective and objective analyses of regional wall motion for asynergic segments showed that all but 4 of 61 segments identified as asynergic with the hemiaxis method were judged asynergic subjectively. However, 15 segments judged asynergic subjectively were judged normal with the hemiaxis method. With the objective method, 29 of 61 asynergic segments (25 percent) were judged improved by 20 percent or more.

Analysis of variance did not demonstrate any difference in patients with stable or unstable angina in the degree of preoperative asynergy or in changes that occurred postoperatively.

Hemodynamic changes: There was no significant change postoperatively in the mean preoperative values for left ventricular end-diastolic pressure (14 ± 6 mm Hg), heart rate (73 ± 12 beats/min) or mean arterial pressure (86 ± 14 mm Hg). There was no significant postoperative change in the mean preoperative ejection fraction, either in the entire series of 51 patients (60.8 ± 15.6 percent, range 27 to 85 percent) or in the 34 patients with at least one asynergic segment (51.7 ± 12.4 percent). The normal ejection fraction for this laboratory is 69 ± 8 percent. Ejection fraction improved (from 49 ± 11.4 to 56.6 ± 14.2 percent, $P < 0.01$) in the 16 patients who had improvement of at least 10 percent in one or more asynergic segments.

Discussion

Results of previous studies on left ventricular function after coronary bypass: In our study a significant number of asynergic left ventricular segments showed improved contraction 1 to 2 years after coronary bypass surgery. Prior studies of the influence of coronary bypass surgery on left ventricular function have shown variable results. Notable improvements in left ventricular function, as judged by a decrease in the left ventricular end-diastolic pressure and improvement in the left ventricular maximal rate of rise of left ventricular pressure (dP/dt), ejection fraction and asynergy were noted by Chatterjee et al.[1,2] in patients studied 2 weeks after operation. Part of the early improvement in left ventricular function in these patients may have been secondary to increased circulatory or neurally released catecholamines present in the immediate postoperative period and reflected by the significant increase in heart rate and high cardiac output observed

TABLE III

Objective Analysis of Left Ventricular Segmental Wall Motion After Coronary Bypass Surgery

	Anterobasal	Anterolateral	Apical	Inferior	Posterobasal
Normal values (% shortening*)	54 ± 8	41 ± 10	12 ± 5	60 ± 15	36 ± 10
Normal segments (% shortening*)					
Preop	52 ± 12	51 ± 17	14 ± 10	61 ± 19	31 ± 11
Postop	47 ± 15	47 ± 16	14 ± 8	59 ± 17	31 ± 11
no. of segments	38	36	43	37	40
P	<0.05	NS	NS	NS	NS
Asynergic segments (% shortening*)					
Preop	29 ± 9	9 ± 6	−1 ± 2	18 ± 8	7 ± 6
Postop	41 ± 15	19 ± 15	9 ± 10	33 ± 25	16 ± 17
No. of segments	13	15	8	14	11
P	<0.002	0.05	0.02	0.02	0.02

* Values stated are mean percent segmental shortening ± 1 standard deviation.
NS = not significant; *P* = probability; Postop = postoperatively; Preop = preoperatively.

postoperatively.[9] Chatterjee et al.[3] later reported significant improvement in left ventricular ejection fraction, wall motion, anginal threshold determined by pacing, as well as regional and global lactate metabolism, in seven patients studied 2 weeks to 6 months after coronary bypass surgery with all grafts patent. Bourassa et al.[4] showed that patent grafts resulted in early (2 weeks) improvement in regional left ventricular asynergy that persisted in patients studied 1 to 2 years after operation. Fifty-one percent of all asynergic segments in their study showed improvement in the 1st year after operation. They also demonstrated significant deterioration in wall motion with incomplete revascularization (that is, graft closure, graft stenosis or progression of disease in the distal coronary artery that was grafted). Improvements in regional left ventricular asynergy after successful bypass surgery with documented graft patency were also reported by Popio et al.[5] and Helfant et al.[6]

In contrast, Hammermeister et al.,[7] who studied 40 patients a mean of 4 months postoperatively, demonstrated variable changes in left ventricular function at rest. They reported a 79 percent graft patency rate and a 20 percent perioperative infarction rate, compared with 95 and 6 percent, respectively, in our series. Contraction plots of left ventricular silhouettes were said to show no change in 25 patients, improvement in 6 patients and deterioration in 9 patients. Griffith et al.[8] reported on 71 patients studied a mean of 6 months after operation with a graft patency rate of 66 percent and an unstated perioperative infarction rate. Segmental wall motion judged subjectively was considered improved in 12 percent, unchanged in 50 percent and worse in 38 percent of the segments. Of the 69 segments supplied by patent grafts, wall motion was judged improved in 18, unchanged in 27 and worse in 24. In contrast to our study, Griffith et al. demonstrated a high rate of distal progression of disease in arteries with patent grafts. In their late study, 20 of 68 coronary arteries with patent grafts had minimal or no visualization in the distal vessel, whereas 8 additional arteries had new narrowings of 50 percent or more in the distal segment not seen preoperatively.

Variability in the reported results of the influence of coronary bypass surgery on left ventricular function may reflect in part differences in selection of patients, timing of the study and surgical skill as reflected in mortality, perioperative infarction and graft patency rates. Our study, in comparison with those of Chatterjee et al.,[1–3] did not demonstrate as extensive an improvement in regional wall motion. This difference may reflect the fact that their patients were studied early after operation. It does not seem to be a result of the large number of patients with unstable angina in their study because we found no significant differences in the results of surgery in patients with unstable versus stable angina pectoris. However, we found greater improvement in wall motion than in that reported by Hammermeister et al.[7] and Griffith et al.,[8] perhaps because of the higher graft patency rate and the lower perioperative infarction rate in our study. Perhaps the most important aspect in the reversibility of left ventricular asynergy, given a successful revascularization, is whether the abnormally contracting segment reflects myocardial ischemia or irreversible infarction or fibrosis.[10]

Factors affecting reversibility of left ventricular asynergy: The identification of reversible asynergy with use of postextrasystolic potentiation[5] or nitroglycerin[6] has provided an important advance in defining those patients who might be expected to have significant reversal of left ventricular dysfunction after successful bypass grafting. Almost all left ventricular segments except those severely fibrosed or infarcted appear to improve on the beat after a premature ventricular contraction.[5] Popio et al.[5] showed that postextrasystolic improvement in left ventricular asynergy in the preoperative ventriculogram is predictive of improvement in contraction after successful surgery. They also demonstrated that the presence of electrocardiographic proof of prior myocardial infarction or the degree of asynergy was not predictive of reversal of left ventricular dysfunction. Similarly, in our series, many segments showed improvement, although the preoperative electrocardiogram indicated that there were regions of previous transmural myocardial infarction. In contrast to some of the previous studies, deterioration of left ventricular contraction after operation was not common in our series; this may have reflected the higher graft patency rate, apparent low rate of progression of distal coronary artery disease and low rate of perioperative infarction.

Of the nine segments that were normal preoperatively and judged worse postoperatively, seven were supplied by patent grafts. In three of these segments, perioperative infarction was clearly documented by new electrocardiographic Q waves. Bulkley and Hutchins,[11] in an autopsy series, recently demonstrated transmural myocardial necrosis in regions supplied by patent grafts into severely stenosed coronary arteries. They suggested that reinstitution of normal flow to low flow ischemic areas may result in cell damage similar to that seen during reflow experiments.[12] In the series of Bulkley and Hutchins, occluded saphenous vein grafts frequently did not result in myocardial necrosis. They suggested that in a newly occluded artery, collateral circulation established before operation may serve a protective function. In our series, although the number of graft occlusions was small, all segments supplied by occluded grafts were unchanged.

Objective versus subjective analysis of ventricular wall motion: Only minor differences were noted between the objective and subjective methods of analyzing regional left ventricular wall motion. Significant interobserver variability in the interpretation of wall motion abnormalities is well known and reflects the potential limitations of subjective analysis.[13] Precision in defining wall motion abnormalities and their change after operation may be greater with objective methods, although this has not been studied. The subjective method, by broadly classifying abnormal wall motion into three categories—hypokinetic, akinetic and

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dyskinetic—may not be sensitive enough to detect the smaller postoperative changes in wall motion detected with the objective method. However, it is not clear that small changes in left ventricular motion demonstrated with objective methods have clinical significance. It is also conceivable that in some cases the objective method used in our study, in which wall motion in each region is represented by two hemiaxes (or one long axis in the case of the apex), may be inadequate to describe completely segmental motion. The subjective method uses the complete perimeter of a segment to detect motion and may in some instances be more accurate.

Role of propranolol: Although almost all patients were taking propranolol before their preoperative catheterization, few were taking propranolol during their postoperative catheterization. It is unlikely that improvement of asynergy postoperatively reflects the absence of propranolol because work from our laboratory[14] has shown that propranolol given intravenously in a dose of 0.15 mg/kg body weight produced no significant effects on regional wall motion and ejection fraction. Furthermore, Marshall et al.[15] reported no significant change in ejection fraction or regional wall motion abnormalities using the gated blood pool scan in patients taking propranolol over long periods.

In summary, this study demonstrates that 1 to 2 years after successful coronary arterial bypass surgery characterized by a low perioperative infarction rate and a high graft patency rate, left ventricular asynergy may improve.

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Reversal of Exertional Hypotension After Coronary Bypass Grafting

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A decrease in systolic blood pressure that occurs with treadmill exercise testing may be a sign of reversible ischemic left ventricular dysfunction. To test this hypothesis, we examined retrospectively the postoperative treadmill responses of 37 patients who had exertional hypotension (end exercise systolic blood pressure less than or equal to initial preexercise levels) before coronary arterial bypass grafting. This group of 37 patients was characterized preoperatively by an abnormal exercise electrocardiogram (36 patients), multiple vessel occlusive disease (36 patients) and a normal ejection fraction at rest (32 patients). Postoperative exercise tests showed improvement in hemodynamic and electrocardiographic changes with reversal of exertional hypotension (33 patients), and conversion to a normal exercise electrocardiogram (29 patients). Coronary bypass surgery can be expected to reverse exertional hypotension in patients with symptomatic angina pectoris and evidence of ischemia in the exercise electrocardiogram.

The normal hemodynamic response to upright treadmill exercise includes a sustained increase in systolic blood pressure.[1] An abnormal decrease in systolic blood pressure occurs during treadmill exercise in a subgroup of patients with coronary atherosclerosis; this decrease may, in part, be caused by acute ischemic left ventricular dysfunction.[2,3]

Coronary bypass surgery improves the functional status of patients with angina. This improvement has been corroborated by data obtained during objective testing with treadmill exercise,[4,5] atrial pacing[6] and measurement of lactate extraction across the myocardium.[7,8] Revascularization of ischemic myocardium might also be expected to improve abnormal exercise hemodynamic responses. We tested this hypothesis by analyzing the postoperative treadmill test results in a subgroup of patients with symptomatic angina pectoris who demonstrated exertional hypotension before coronary bypass grafting.

Methods

Patients: Thirty-seven patients who manifested exertional hypotension during preoperative treadmill exercise testing constituted the study group. There were 32 men and 5 women with a mean age of 55 years (range 40 to 70). These patients were retrospectively identified from a consecutive series of 360 patients undergoing isolated coronary arterial bypass surgery for symptomatic angina pectoris between October 1974 and January 1978 at this institution (1 patient in this group [0.28 percent] died within 30 days of operation). Preoperative treadmill exercise tests were performed in 234 patients of whom 55 (24 percent) had exertional hypotension, defined as an end systolic blood pressure equal to or less than the preexercise standing level. Eighteen of the 55 patients were excluded from the study because they lacked a postoperative test or were receiving propranolol, antihypertensive drugs, digitalis or diuretic drugs at the time of preoperative testing.

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TABLE I

Summary of 37 Cases

	Preoperative Data									
Case no.	EF	CAD	SBP at Rest	HR at Rest	ΔSBP	ΔHR	RPP	Exercise Time (min)	FAI	Exercise ECG
1	0.70	3	130	74	−50	+29	94	2.8	63	Abnormal
2	0.81	2	155	88	−70	+62	128	3.2	40	Abnormal
3	0.62	3*	124	85	−44	+65	184	1.6	85	Abnormal
4	0.39	2	142	108	−58	+22	109	3.3	62	Abnormal
5	0.83	2	165	80	−45	+45	150	4.0	50	Abnormal
6	0.58	3*	144	86	−34	+59	160	5.0	42	Abnormal
7	0.60	3*	150	66	−40	+62	141	5.3	40	Abnormal
8	0.80	2	152	58	−48	+100	225	2.8	40	Abnormal
9	0.70	3*	178	96	−23	+65	218	2.8	57	Abnormal
10	0.82	3*	165	120	−10	+22	220	7.2	15	Abnormal
11	0.40	3*	130	88	−10	+57	194	4.8	38	Abnormal
12	0.82	2	148	75	−18	+85	268	7.7	20	Abnormal
13	0.81	3	132	98	−2	+22	156	3.5	62	Abnormal
14	0.82	3*	160	100	0	+55	248	3.0	68	Abnormal
15	0.68	3	134	75	−2	+140	151	3.7	54	Abnormal
16	0.67	3	130	98	−14	+72	197	7.6	28	Abnormal
17	0.47	3	148	75	−20	+67	182	2.1	80	Abnormal
18	0.69	3	130	94	−28	+91	189	3.4	62	Abnormal
19	0.45	2	130	90	−20	+43	151	2.7	72	Abnormal
20	0.21	3	116	72	−6	+68	154	2.8	63	Abnormal
21	0.73	3	120	78	−10	+54	145	4.8	50	Abnormal
22	0.72	2	180	94	−6	+76	295	7.0	24	Abnormal
23	0.67	3	118	75	−34	+57	110	3.1	67	Abnormal
24	0.72	3*	138	76	0	+98	237	6.6	18	Abnormal
25	0.74	3*	100	74	−10	+70	144	6.9	19	Abnormal
26	0.57	3*	170	73	−40	+117	247	6.5	33	Abnormal
27	0.72	1	156	56	−14	+104	227	8.3	−1	Abnormal
28	0.63	3	110	65	−30	+57	98	4.6	45	Abnormal
29	0.33	3	140	100	−20	+50	180	6.3	30	Abnormal
30	0.74	3	140	86	−30	+56	156	5.1	20	Abnormal
31	0.69	3	154	70	−54	+75	145	6.7	22	Abnormal
32	0.91	2	152	70	−2	+80	222	2.0	61	Abnormal
33	0.57	3*	148	99	−4	+61	230	5.2	50	Abnormal
34	0.52	2	124	55	−4	+85	168	6.3	30	Abnormal
35	0.60	3	140	70	0	+30	140	3.0	68	Abnormal
36	0.63	3*	160	104	0	+44	236	4.7	28	Abnormal
37	0.86	3*	146	76	−38	+54	140	4.4	48	Abnormal

* Left main coronary arterial stenosis.
CAD = coronary artery disease (no. of vessels involved); EF = ejection fraction; FAI = functional aerobic impairment; HR = heart rate (beats/min);

Exercise testing: All patients in the study group performed exercise according to the Bruce multistage protocol.[9] Cuff blood pressures were measured at 1 minute intervals with a mercury-calibrated anaeroid sphygmomanometer. The highest systolic blood pressure and heart rate within each 3 minute interval and the final values at the end of exercise were recorded. A 12 lead electrocardiogram was continuously recorded during and for 9 minutes after exercise.

The difference between the last systolic blood pressure recorded during exercise and the initial standing preexercise systolic blood pressure was calculated for each patient; rate-pressure product and functional aerobic impairment were derived from exercise data as additional performance indexes.

Postoperative testing was performed within 9 months (mean 3.7) after operation. The statistical significance of differences observed for each performance index was calculated by a paired *t* test.

An abnormal exercise electrocardiographic response was defined as a flat or downsloping S-T segment depression equal to or greater than 1 mm and of 0.08 second duration in at least three consecutive complexes, occurring during or after exercise. When the resting electrocardiogram showed S-T depression, these criteria were doubled, with a 2 mm depression below baseline required to define an abnormal response. A borderline response was either a flat S-T segment of less than 1 mm depression or a junctional upward sloping S-T segment that remained 1 mm below baseline at 0.06 to 0.08 second after the J point in the postexercise tracing.

Cardiac catheterization and operation: Selective coronary arteriograms were performed in multiple projections and recorded on 35 mm cine film. An occlusive lesion greater than 50 percent of vessel diameter was considered critical. A single plane left ventriculogram was obtained in the right anterior oblique projection before coronary angiography, and ejection fraction was calculated by the area-length method.[10]

Our previously described techniques[11] *of coronary bypass grafting* were employed with exclusive use of an autogenous saphenous vein. The average number of grafts placed per patient was 2.8. One patient received a single graft, 10 patients received two grafts, 23 received three grafts, two received four grafts, and one received five grafts.

TABLE I (continued)

Summary of 37 Cases

			Postoperative Data					
Case no.	SBP at Rest	HR at Rest	ΔSBP	ΔHR	RPP	Exercise Time (min)	FAI	Exercise ECG
1	128	78	+44	+87	283	9.3	2	Normal
2	138	100	+18	+65	257	6.8	−12	Normal
3	130	68	+20	+100	252	7.3	25	Normal
4	130	90	+30	+90	228	9.5	−12	Normal
5	180	58	+50	+112	391	9.3	−12	Normal
6	128	90	+28	+90	280	9.4	−3	Normal
7	144	92	+42	+70	301	9.9	−12	Normal
8	142	101	+68	+68	354	6.3	−20	Normal
9	120	75	+40	+76	275	8.7	−7	Normal
10	156	112	+74	+79	414	11.2	−25	Normal
11	142	110	+56	+70	374	7.8	7	Normal
12	130	73	+50	+109	327	9.1	11	Normal
13	128	105	+66	+75	349	9.5	−2	Normal
14	160	99	+70	+81	414	6.1	−3	Normal
15	138	90	+42	+63	275	7.0	12	Normal
16	114	96	+42	+94	296	10.8	0	Borderline
17	148	90	+6	+80	261	8.4	14	Borderline
18	128	103	+62	+69	326	7.3	16	Normal
19	152	105	+60	−75	381	9.7	0	Normal
20	128	78	+60	+102	338	9.1	−12	Borderline
21	110	94	+40	+76	255	9.5	−2	Normal
22	164	78	+50	+112	410	9.4	0	Normal
23	104	94	+76	+86	324	9.8	−7	Normal
24	140	94	+66	+91	381	6.8	15	Normal
25	120	74	+14	+96	227	8.8	−6	Normal
26	130	118	+60	+72	361	9.1	7	Normal
27	130	65	+58	+80	272	9.4	−17	Borderline
28	120	94	+34	+66	246	8.4	0	Normal
29	140	104	+40	+68	309	9.3	−3	Normal
30	138	90	+62	+80	340	6.3	0	Abnormal
31	144	74	+40	+106	331	8.4	−1	Abnormal
32	152	98	+28	+67	284	3.0	49	Abnormal
33	144	69	+10	+99	258	7.6	22	Abnormal
34	130	70	0	+83	198	5.2	40	Abnormal
35	124	90	−6	+48	165	4.8	41	Abnormal
36	146	105	−36	+45	165	4.0	43	Abnormal
37	160	82	0	+68	204	7.2	14	Abnormal

ΔHR = end exercise heart rate − heart rate at rest; RPP = rate-pressure product = systolic blood pressure × heart rate × 10^{-2}; SBP = systolic blood pressure (mm Hg); ΔSBP = end exercise systolic blood pressure − resting systolic blood pressure.

One perioperative myocardial infarct occurred (3 percent). This was a nontransmural infarction occurring 4 days after double vein grafting (Table I, Patient 32).

Results

The results of cardiac catheterization and treadmill exercise testing for all 37 patients are listed in Table I.

Preoperative cardiac catheterization: Multiple vessel involvement was present in most of the 37 patients. Triple vessel disease was present in 27 patients (73 percent), double vessel disease in 9 patients (23 percent) and single vessel disease in only 1 patient. Critical left main coronary arterial stenosis was present in 13 patients (35 percent). With involvement of the left main coronary artery counted as double vessel disease, the average number of jeopardized major vessels per patient was 2.7. Five patients had impaired left ventricular systolic pump function with an ejection fraction of less than 0.50 (Table I). The mean ejection fraction was normal (0.65). Left ventricular end-diastolic pressure ranged from 2 to 26 mm Hg (mean 10) before ventriculography and from 5 to 36 mm Hg (mean 18) afterward.

Stress tests: Table II lists the mean values, standard errors and statistical significance of the pre- and postoperative performance indexes listed in Table I. The mean change in the difference between the last and preexercise systolic blood pressure values (ΔSBP) before operation was −23 mm Hg and after operation was +40 mm Hg; the net postoperative increase in ΔSBP of 63 mm Hg was highly significant (Fig. 1). The observed changes in heart rate, rate-pressure product and functional aerobic impairment also showed significant increases.

Whereas all patients had abnormal electrocardiographic exercise responses preoperatively, the postoperative tracings were normal in 25 patients, borderline

TABLE II

Pre- and Postoperative Treadmill Exercise Performance Indexes in 37 Patients

Performance Index*	Preoperative	Postoperative	P Value
ΔSBP (mm Hg)	−23 ± 3	+40 ± 5	<0.001
ΔHR (beats/min)	+64 ± 4	+81 ± 3	<0.005
Rate-pressure product	179 ± 8	300 ± 11	<0.001
Duration of exercise (min)	4.6 ± 0.3	8.1 ± 0.3	<0.001
Functional aerobic impairment (%)	45 ± 7	4 ± 3	<0.001

* Mean values ± standard error.
P = probability.

in 4 and remained abnormal in 8. Preoperative treadmill tests were terminated because of limiting angina pectoris in 20 patients, marked electrocardiographic changes in 3 and decreasing systolic blood pressure in 14. No infarct occurred as a result of exercise testing.

Postoperatively, angina was absent in 25 patients who had a normal exercise electrocardiogram. Six of 12 patients with a persistently abnormal or borderline postoperative exercise electrocardiogram experienced exercise-induced angina (Patients 32 to 37), whereas only 2 patients (Patients 30 and 31) had an abnormal exercise electrocardiogram but did not experience angina. The reasons for terminating exercise postoperatively were angina in 6 patients and nonspecific symptoms of fatigue, dyspnea and leg weakness in the remaining 31.

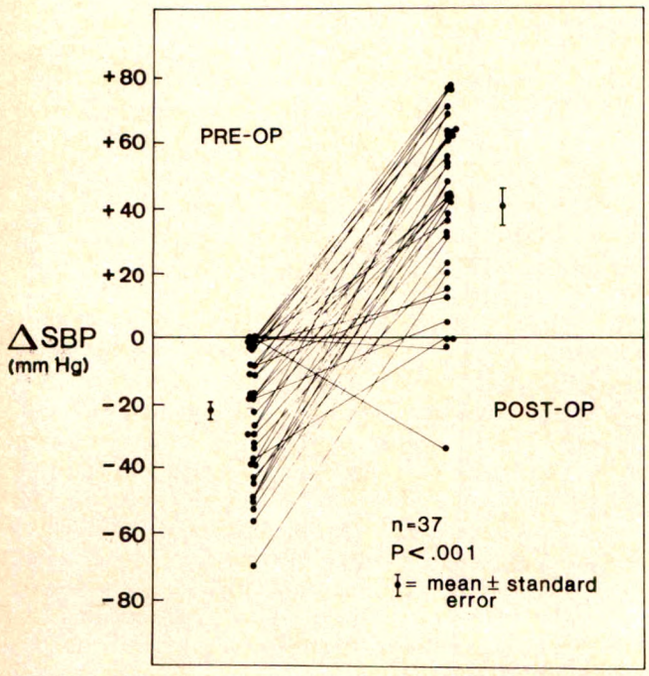

FIGURE 1. Effect of coronary bypass surgery in 37 patients. The change in systolic blood pressure (ΔSBP) with exercise for each patient is shown before and after operation. The mean change in ΔSBP was −23 mm Hg preoperatively (PRE-OP) and +40 mm Hg postoperatively (POST-OP). n = number of patients; P = probability.

Five of the six patients who had exertional angina postoperatively underwent repeat angiography (Table III). Occlusion of one graft, progressive disease in the native vessels or distal occlusive disease with patent grafts, alone or in combination, were found in these patients.

Discussion

Clinical significance of exertional hypotension: A decrease in systolic blood pressure that occurs early during exercise testing is a useful clinical observation.[12] This abnormal hemodynamic finding was first described by Bruce et al.,[13] who speculated that impaired cardiac function was a causative mechanism whenever hypovolemia or impaired vasomotor tone was absent. Exercise-induced hypotension in patients with coronary atherosclerosis has been described in association with multiple vessel disease and has been attributed to ischemic left ventricular dysfunction.[2,3] Studies employing radionuclide ventricular exercise scanning tend to support this conjecture.[14,15]

The prognostic implication of such abnormal exercise blood pressure responses is not clear, although patients whose maximal systolic blood pressure is 140 mm Hg or less appear to have a greater incidence of subsequent sudden cardiac death.[16] The prevalence of hypotensive exercise responses among patients with symptomatic coronary atherosclerosis is generally unknown because of failure to measure blood pressure during routine treadmill testing. Spontaneous reversal or reversal under medical therapy has not been reported.

Postoperative reversal of exertional hypotension: Reversal of exercise-induced blood pressure abnormalities after coronary arterial bypass surgery has been observed in a few patients.[2,3] We chose to examine in detail the treadmill test results in a large group of patients and select for analysis those patients showing grossly abnormal preoperative hemodynamic responses. All patients in our group had exertional hypotension; that is, none had a systolic blood pressure at the end of maximal exercise greater than the preexercise value. No patient had associated valvular heart disease or primary cardiomyopathy or was receiving medications that could influence the adaptive mechanisms that normally occur during exercise to maintain sustained increases in systolic blood pressure.

All patients in our study group with exertional hypotension had an abnormal exercise electrocardiogram and all but one had multiple vessel disease. Only six had an ejection fraction at rest of less than 0.50. Thus, exertional hypotension was far more frequently associated with exertional myocardial ischemia than with permanent myocardial damage. Moreover, after coronary bypass surgery, most patients had reversal of both exertional hypotension and electrocardiographic abnormalities, suggesting that exertional hypotension was both temporary and reversible. When exertional hypotension persisted postoperatively, it was always associated with either incomplete revascularization or

TABLE III

Postoperative Catheterization Data on Five Symptomatic Patients

Case no.	Weeks From Operation To Postoperative Study	EF	LVEDP	Arteriographic Findings
32	2	0.66	0–16	Occluded circumflex marginal graft; patent right coronary bypass graft
33	6	0.66	4–7	Occluded graft to right coronary artery; patent graft to left anterior descending and circumflex coronary arteries
34	8	0.68	15–20	Patent left anterior descending graft to diffusely diseased vessel; 50% distal right main stenosis not visualized on initial study
35	9	0.35	—	Occluded graft to circumflex descending coronary artery; patent graft to left anterior descending coronary artery; interval occlusion circumflex coronary artery; interval occlusion of nondominant right coronary artery
36	16	0.77	7–11	Patent anterior descending graft; patent circumflex marginal graft; interval occlusion of circumflex marginal artery; interval distal stenosis of left anterior descending artery

EF = ejection fraction; LVEDP = left ventricular end-diastolic pressure (mm Hg).

progression of disease and was not related to poor postoperative ventricular function.

Postoperative graft angiography was not routinely employed in this study because most patients were asymptomatic and had a normal exercise electrocardiogram. A good correlation has been demonstrated between coronary bypass graft patency and conversion of an abnormal to a normal exercise electrocardiogram.[17] Improvement in treadmill performance in patients with all grafts occluded has been observed and associated with either perioperative myocardial infarction or far less severe coronary occlusive disease.[18] Reversal of exertional hypotension after totally unsuccessful revascularization has not been reported or, in our experience, observed.

The natural history of patients with coronary atherosclerosis and exertional hypotension is not known. Thus, although reversal of exertional hypotension appears to be a desirable result of coronary bypass surgery, whether it contributes to longevity remains unknown. Nevertheless, it appears to be a good index of alleviation of exertional myocardial ischemia.

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Improved Survival Beyond 5 Years After Coronary Bypass Surgery in Patients With Left Main Coronary Artery Disease

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To determine the truly late survival of surgically treated patients with left main coronary arterial stenosis, the fate of 134 consecutive patients with greater than 50 percent stenosis of the luminal diameter of the main left coronary artery who underwent coronary bypass surgery between 1968 and 1973 was determined. Eighty-seven percent (117 or 134) of the patients were men; the mean age was 57 years (range 37 to 70). In addition to left main stenosis, coexistent significant coronary disease was present in other vessels in 128 patients (95.5 percent), with multivessel disease present 109 (81 percent). Ventricular function was good (end diastolic pressure less than 15 mm Hg and no localized contraction abnormality) in 88 patients (66 percent) and poor in 46 patients (34 percent). The perioperative mortality rate was 13 percent (17 patients) in the total group and 11 percent (10 of 88) among patients with good left ventricular function. Postoperative graft patency in 33 patients was 85 percent (58 of 68). All patients were followed up at least 5 years after operation. The survival rate was 79 percent (106 of 134) for the total group, 81 percent (71 of 88) in patients with good ventricular function and 76 percent (35 of 46) in patients with poor ventricular function. Late annual attrition rates were 1.5 percent and 2.1 percent for patients with good and poor ventricular function, respectively. Comparison of these results with the normal U. S. population of identical age and sex distribution indicates that late attrition (excluding perioperative mortality) is almost normal after operation for patients with good ventricular function. Since this early experience between 1968 and 1973, results have improved markedly. These results indicate that excellent long-term survival can be obtained from operation in these patients with severe disease.

There has been little information on the truly long-term fate of patients with left main coronary arterial stenosis who have been treated with coronary bypass surgery. For this reason we attempted to determine the survival of a group of these patients who were treated by operation and had a full 5 years of follow-up.

Methods

Patients: Between 1968 and 1973, a total of 134 consecutive patients with more than 50 percent reduction in luminal diameter of the left main coronary artery underwent saphenous vein aortocoronary bypass surgery. No patients were excluded retrospectively from this series, and both elective and emergency operations were included. There were 117 men (87 percent). The mean age at operation was 57 years (range 37 to73). All patients were operated upon because of angina pectoris unresponsive to medical therapy. A history of previous acute myocardial infarction was given by 80 of the 134 patients (59.7 percent), and 43 (32 percent) had Q wave or S-T segment abnormalities in the electrocardiogram obtained at rest.

Associated coronary artery disease: Left main coronary arterial stenosis was rarely an isolated lesion: only 6 (4.5 percent) of the 134 patients had left main

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disease alone. There was one associated coronary stenosis of more than 70 percent luminal diameter reduction in 19 patients (14 percent), two lesions in 49 (37 percent) and three lesions in 60 (45 percent). Thus, there was associated severe multivessel disease in 109 patients (81 percent). The right coronary artery was severely stenosed in 100 patients (75 percent).

Ventricular function: Left ventricular function was defined as good if the end-diastolic pressure was less than 15 mm Hg and there was no akinetic or aneurysmal area in the left ventriculogram. Poor ventricular function was said to be present if the end-diastolic pressure was more than 15 mm Hg or an akinetic or aneurysmal area was present in the ventriculogram, or both. By these criteria, 88 of the 134 patients (68 percent) had good left ventricular function and the remaining 46 (34 percent) had poor left ventricular function. Of these 46 patients, 21 (46 percent) had severe elevation of end-diastolic pressures in the range of 25 to 55 mm Hg and 7 (15 percent) had a left ventricular aneurysm.

All operations were performed under one period of normothermic ischemic arrest utilizing normothermic dilution-prime cardiopulmonary bypass. An average of 2 grafts were performed in each patient.

Follow-up: Survival was determined at a follow-up period of at least 5 years in all cases. Follow-up was complete in 131 patients (98 percent), and this was the result of regular long-term patient contact by letter or office visit. The remaining patients were contacted by telephone or their survival status was determined by professional investigators. The three missing patients were assumed to be alive.

For comparison, the survival was determined of a consecutive series of 73 patients with left main coronary arterial stenosis operated on between 1976 and 1978 in which the follow-up was 100 percent. Except for a slightly lesser prevalence of impairment of left ventricular function in the later group, the two groups of patients were similar (Table I).

Results

Perioperative mortality and infarction: Overall perioperative mortality (30 day) was 13 percent (17 of 134). It was 11 percent (10 of 88) in patients with good left ventricular function and 15 percent (7 of 46) in patients with poor left ventricular function. The most common cause of death was perioperative myocardial infarction (13 of 17). The perioperative infarction rate in the survivors as measured by the appearance of new Q waves in the electrocardiogram was 5 percent (6 of 117).

Late survival: At a follow-up period of at least 5 years in all cases and including deaths from all causes, overall late survival (including perioperative mortality) was 79 percent (106 of 134). The survival rate was 81 percent (71 of 88) and 76 percent (35 of 46) for patients with good and poor ventricular function, respectively (Fig. 1). With exclusion of perioperative mortality, the late annual attrition rates were 1.5 and 2 percent, respectively, for the groups with good and poor ventricular function. For a sample of the general population of 1973 aged 56 years, with a sex distribution identical to that of our patients, the annual attrition rate from all causes was 1.3 percent.[1]

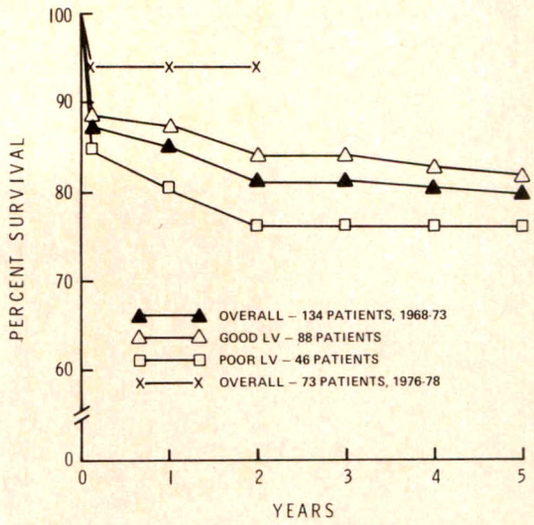

FIGURE 1. Overall survival curves of the early and late groups of patients treated by operation. Survival of the early group is shown also according to preoperative left ventricular (LV) function as defined in the text.

Influence of associated coronary artery disease: Perioperative mortality and late survival were uninfluenced by the presence or absence of right coronary arterial stenosis. In the 100 patients with right coronary stenosis, the perioperative mortality rate was 13 percent and the overall survival rate was 78 percent. Survival was also uninfluenced by the number of associated coronary stenoses present or by the presence or absence of high grade left main coronary stenosis (more than 70 percent reduction of luminal diameter) (Table II).

TABLE I

Comparisons of the Early and Late Groups of Surgically Treated Patients

	1968–1973	1976–1978
Mean age (yr)	57	59.5
Sex (% male)	87	86
Incidence of multivessel disease (%)	81	86
Incidence of poor left ventricular function (%)	34	21
Perioperative mortality (%)	13	5.5
Left ventricular function (%)		
Good	11	7
Poor	15	0

TABLE II

Overall Absolute 5 Year Survival Rates According to the Number of Associated Severe Coronary Lesions and the Presence of Good or Poor Left Ventricular Function

CAD†	Ventricular Function		
	Good	Poor	Overall
0	67%(4/6)	—	67%(4/6)
1	100%(12/12)	43(3/7)	79%(15/19)
2	81%(26/32)	88%(15/17)	84%(41/49)
3	76%(29/38)	77%(17/22)	77%(46/60)
Overall	81%(71/88)	76%(35/46)	79%(106/134)

† CAD = coronary artery disease; 0, 1, 2, 3 indicate the number of vessels diseased in addition to the left main coronary artery.

Graft patency: Thirty-three patients underwent follow-up coronary angiography 1 to 75 months after operation. The overall graft patency rate was 85 percent (58 of 68 grafts); at least 1 graft was patent in 97 percent of the 33 patients and all grafts were patent in 76 percent.

Comparison with 1976–1978 surgical group: In the 73 consecutive patients with left main coronary artery disease operated on between 1976 and 1978, the perioperative mortality rate (30 day) was 5.5 percent (4 of 73), and all deaths were intraoperative. However, two of these four deaths were in patients brought to the operating room from the cardiac catheterization laboratory with no spontaneous cardiac output. Thus, in the remaining 71 elective cases, the perioperative mortality rate was 3 percent (2 patients). At autopsy these two patients had evidence of recent acute myocardial infarction of more than 24 hours' duration that had not been diagnosed preoperatively. There were no late deaths in the 69 survivors up to 24 months after operation.

Discussion

Prognosis of patients with left main coronary artery disease: Although there have been several reports[2–7] documenting the favorable early results of operation for left main coronary artery disease, the advanced nature of the coronary disease in these patients makes determination of their late survival of some importance. The reported survival rates of such patients treated with medical therapy are dismal. Survival rates of selected groups of patients whose condition was considered operable but who were treated medically range from 50 to 64 percent[2,4,8] at follow-up intervals of 2 to 4 years (Fig. 2). Even in a highly selected "low risk" subgroup defined by Conley et al.[9] by the absence, or presence of only one of four risk factors: a history of congestive heart failure, chest pain at rest, cardiomegaly on chest X-ray examination or ST-T wave changes in the resting electrocardiogram, survival at 36 months was only 74 percent (Fig. 2).

Role of state of left ventricular function in surgical results: The extremely low late annual attrition rate observed in our patients with good preoperative left ventricular function who survived operation has approximated that of the general U. S. population of the same age and sex. Furthermore, at a complete follow-up period of more than 5 years there has been no deterioration of the late attrition rate despite the severity of coronary artery disease in these patients (Fig. 1).

The state of left ventricular function as we have defined it seemed to exert a smaller influence on late survival in this group of patients than in our overall experience, in which we have observed a substantial difference in late survival in the two groups.[10,11] This apparent lack of influence may be due to the very high perioperative mortality rate in this early experience which exceeded the subsequent total late attrition both in the group with good and the group with poor ventricular function. This high perioperative mortality rate was due primarily to the pre- and intraoperative instability before bypass produced by the left main coronary arterial lesion rather than the state of left ventricular function as such. That high mortality occurred in both groups of patients is also quite different from our overall experience,[11] in which the perioperative mortality rate was substantially lower in patients with good ventricular function. We believe that this further emphasizes the predominant influence of the left main coronary arterial lesion itself on the fate of these patients.

Recent improvements in medical and surgical treatment: The marked improvement in surgical results in our more recent experience is due to multiple factors. In these patients we now believe that medical stabilization is important before cardiac catheterization and should include maintenance of propranolol therapy at full dosage. Cardiac catheterization should be as brief as possible, and should be concluded quickly once the

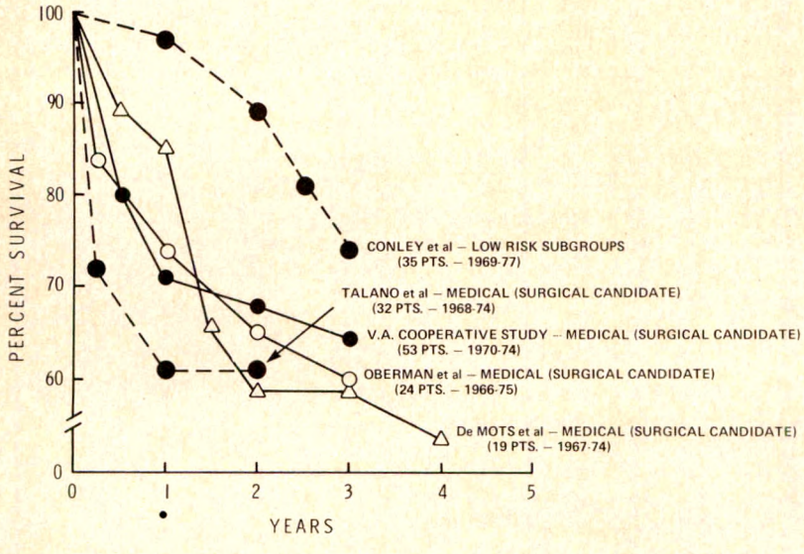

FIGURE 2. Survival curves of selected groups of medically treated patients with more than 50 percent stenosis of the left main coronary artery. See texts for references. PTS = patients; V.A. = Veterans Administration.

coronary lesions have been identified. Patients showing any signs of instability are treated with aggressive medical therapy, particularly nitrates and intravenous propranolol. Such precautions have led to a substantial reduction in the number of patients brought from the cardiac catheterization laboratory to the operating room with cardiogenic shock. In patients refractory to medical therapy after cardiac catheterization we still advocate immediate operation rather than insertion of the intraaortic balloon, which we use but rarely.

Once in the operating room, any hypertension or tachycardia is treated with intravenous nitroglycerin or nitroprusside and propranolol. Meticulous control of the heart rate and blood pressure and the rapid establishment of total cardiopulmonary bypass have almost eliminated unexpected hypotension or arrhythmias during induction of anesthesia and before institution of cardiopulmonary bypass.

A major advance in our surgical technique has been the introduction of myocardial preservation with use of cold potassium cardioplegia and topical cardiac hypothermia. This technique has produced a noticeable improvement in the perioperative course of these patients in regard to the incidence of low output syndrome and arrhythmias.

The substantial reduction in perioperative mortality and late attrition rates which we have achieved with increasing experience with this lesion has also been noted by others. Unfortunately, a similar improvement in the results of medical therapy has not been achieved with the passage of time despite the widespread use of modern intensive medical therapy. In both the Veterans Administration Cooperative Study of patients with significant left main coronary arterial lesions[8] and the report of Campeau et al.,[7] survival of the medically treated patients in the early and later experiences was little different whereas the survival of the corresponding surgical groups had improved substantially.

Implications: Our good long-term results are consistent with previous observations of patients operated on for coronary disease without involvement of the left main coronary artery in whom we have documented the late stability of the native circulation, graft patency, left ventricular function and good late annual attrition rates beyond 5 years.[10,11] The very favorable overall late survival and late attrition rates of our patients even in this initial and early experience with left main coronary stenosis have encouraged us to continue to offer surgical therapy to them not only for relief of symptoms but also for long-term prolongation of life.

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Correlation of Thallium-201 Scintigrams With Coronary Anatomy: Factors Affecting Region by Region Sensitivity

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Myocardial perfusion scintigraphy, performed after administration of thallium-201 during exercise, has come into widespread use for evaluating patients with coronary artery disease. Previous studies indicate that it is both sensitive and highly specific. However, thallium-201 scintigraphy evaluates relative rather than absolute perfusion and may therefore be misleading in estimating the extent of coronary disease. This study evaluated the effect of the number and location of diseased vessels, the severity of coronary stenosis and the presence of previous infarction on the overall and regional sensitivity of scintigraphy in 78 patients. The overall sensitivity and specificity levels were 89 and 93 percent, respectively; vessel by vessel, the respective values were 67 and 96 percent. Scintigraphy had greater overall sensitivity in patients with multivessel disease than in those with single vessel disease, but in individual patients the regional sensitivity was not affected by the number of vessels involved. Scintigraphy correctly indicated the number of diseased vessels in only a minority of patients. Left circumflex arterial obstructions were frequently not detected (sensitivity 45 percent compared with 75 percent for other major arteries). Perfusion abnormalities were much more likely to be present (80 versus 39 percent, $P < 0.01$) in the distribution of vessels with severe (more than 90 percent) stenosis than in that of vessels with moderate (70 to 90 percent) stenosis. A greater proportion of both patients and regions with old infarctions were judged scintigraphically abnormal. However, these differences were not significant and reflected only the infarcted regions themselves, because other jeopardized vessels were detected with the same frequency in patients with and without infarction.

The findings indicate that the sensitivity of exercise thallium-201 scintigraphy, despite its relative nature, is not impaired by the presence of widespread coronary disease or areas of old infarction. The most important factor determining the regional sensitivity of scintigraphy is the severity of the corresponding stenosis, and the major factor affecting sensitivity in an individual patient is the number of vessels involved.

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Myocardial perfusion scintigraphy has become increasingly popular as a noninvasive method for detecting and evaluating patients with coronary artery disease. Several groups[1–4] have now reported their experience with thallium-201, the current radionuclide of choice for this application, and with other related agents.[5–8] Most investigators have found that this technique is both highly specific and quite sensitive in the diagnosis of patients with coronary disease.

However, myocardial perfusion scintigraphy is a relative rather than an absolute technique and is capable only of indicating the degree of perfusion of one region of myocardium relative to others. Some ischemic regions supplied by significantly stenosed arteries may therefore appear to be normally perfused in relation to infarcted regions or those supplied

by more severely narrowed vessels. Thus, the sensitivity of scintigraphy in detecting diseased arteries or ischemic regions may be lower in the presence of multivessel involvement or accompanying areas of old infarction. Therefore, this study was undertaken to evaluate the effect of the severity and distribution of coronary arterial involvement and of the presence of areas of previous myocardial infarction on the overall and regional sensitivity of perfusion scintigraphy.

Methods

Patients: The study group consisted of 78 of 100 consecutive patients who underwent both coronary arteriography and myocardial perfusion scintigraphy within a 14 day interval for evaluation of chest pain suggestive of angina pectoris. Patients with unstable angina or recent myocardial infarction were not included. Twenty-two patients were excluded because they were studied after bypass surgery (10 patients) or had a positive exercise scintigram without follow-up resting or redistribution images (10 patients) or their scintigrams were technically inadequate for interpretation (2 patients). The mean age of the included patients was 56 years (range 28 to 71). Fifty-seven were men and 21 were women.

The patients were classified into three groups on the basis of arteriographic findings. Groups 1 and 2 had one or more lesions equal to or greater than 70 percent narrowing of luminal diameter. The 31 patients in Group 1 had no electrocardiographic changes or history suggestive of a previous myocardial infarction. All 33 patients with any clinical or electrocardiographic evidence of previous infarction were included in Group 2. Of these 33 patients, 26 had significant Q waves (duration 0.04 second or greater), 1 had previously manifested inferior lead Q waves that disappeared, 4 had documented subendocardial infarction and 2 gave a history of hospitalization for infarction without any available documentation. Group 3 consisted of the remaining 14 patients with coronary arteries that were either normal or had no stenosis of 70 percent or greater.

Coronary arteriography: The coronary arteriograms were obtained in multiple projections and were interpreted by two observers who were unaware of the scintigraphic findings. Lesions were classified by the maximal degree of narrowing present in any projection as severe (more than 90 percent), moderate (70 to 90 percent) or not significant (less than 70 percent). When the observers disagreed, the final interpretation was arrived at by consensus or by a third reader.

Myocardial perfusion scintigraphy: This procedure was performed with either a Searle Pho-Gamma IV or an Ohio Nuclear Series 120 scintillation camera, equipped initially with a converging and subsequently with a high sensitivity collimator and using a 20 percent window centered at approximately 75 kev. Hepatic and splenic activity were shielded when apparent. The initial image was performed in the anterior projection and was taken to 200,000 counts. Subsequent images in the 45° left anterior oblique and left lateral projections were taken at the same time as those performed in the mitral projection.

Stress perfusion scintigraphy was performed with the patient in the postabsorptive state by injecting 2 mCi thallium-201 through an indwelling intravenous cannula 30 to 60 seconds before completion of treadmill exercise. The treadmill exercise tests, which used a modified Bruce protocol,[9] were symptom-limited and were discontinued only when patients experienced severe chest pain or dyspnea, manifested potentially dangerous arrhythmias or became exhausted. Of the 64 patients with coronary artery disease studied, 42 achieved 85 percent of age-predicted maximal heart rate and 40 manifested electrocardiographic evidence of ischemia (1.0 mm or greater new horizontal or downsloping S-T segment depression by comparison with the preexercise tracing). All but one patient without significant coronary artery disease achieved 85 percent of maximal predicted heart rate, and five patients had ischemic electrocardiographic changes. Scintigraphy was started within 10 minutes of the cessation of exercise and was usually completed within 30 minutes.

Initially, patients with a positive exercise scintigram were restudied at rest within 3 to 14 days (45 of 58 patients). In the last 10 patients imaging was repeated after 3 to 4 hours to assess radionuclide redistribution.[10]

Scintigraphic interpretation and regional analysis: The scintigrams were interpreted independently by two observers who were not aware of the arteriographic findings. When the observers disagreed, a consensus was obtained. One observer reinterpreted scintigrams from 50 patients on a second occasion to assess the reproducibility of the readings. The exercise and resting or redistribution scintigrams were initially read separately and then compared. An exercise scintigram was considered abnormal if any area of decreased perfusion was present. If the defect was also present at rest or unchanged after redistribution, it was considered indicative of previous infarction. New or increased defects were considered evidence of exercise-induced ischemia.

Nine regions in the three projections were individually assessed (*Fig. 1*). The anterior wall (anterior and left lateral projections) and interventricular septum (left anterior oblique projection) were assumed to represent the distribution of the left anterior descending coronary artery; the posterior wall (left anterior oblique projection), the left circumflex distribution; and the inferior wall (all three projections), the distribution of the right coronary artery or a dominant left circumflex artery. An apical abnormality alone was interpreted as indicating coronary artery disease but was not considered specific for involvement of any single vessel.

The results were evaluated for statistical significance with the contingency table method, using the chi square statistic.

Results

Interobserver and intraobserver agreement: Both readers agreed completely on their initial interpretation of the studies in 87 percent of cases (68 of 78). In four cases, they disagreed only on the grading of a

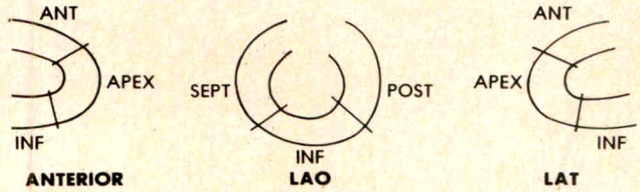

FIGURE 1. Diagrams showing the nine regions, as they were defined in the three scintigraphic projections. The anterior wall (ANT) in the anterior projection and the septal (SEPT) region in the left anterior oblique (LAO) projection were considered to represent the distribution of the left anterior descending coronary artery. The inferior wall (INF) in all three projections was assumed to be supplied by the right coronary artery or a dominant circumflex vessel, and the posterior wall (POST) in the LAO view was assumed to be supplied by the left circumflex artery. Isolated apical defects, although considered indicative of coronary disease, were not considered specific for disease of any single vessel. LAT = lateral.

TABLE I

Scintigraphic Sensitivity in Relation to Extent of Coronary Artery Disease

	Proportion of Patients and Abnormal Vessels Detected Scintigraphically			
	1 VD	2 VD	3 VD	Total
All patients with CAD (No. = 64)				
Patients	11/15 (73%)	13/15 (87%)	33/34 (97%)	57/64 (81%)
Abnormal vessels	11/15 (73%)	20/30 (67%)	67/102 (66%)	98/148 (66%)
Group I, no infarction (No. = 31)				
Patients	4/6 (67%)	6/8 (75%)	16/17 (94%)	26/31 (84%)
Abnormal vessels	4/6 (67%)	9/16 (56%)	30/51 (59%)	43/73 (59%)
Group II, previous infarction (No. = 33)				
Patients	7/9 (78%)	7/7 (100%)	17/17 (100%)	31/33 (94%)
Abnormal vessels	7/9 (78%)	11/14 (79%)	37/51 (75%)	55/74 (74%)

CAD = coronary artery disease; VD = vessels diseased.

single region, and the overall assessment of vessel involvement was not affected. Disagreement about involvement of a vessel occurred in six cases and altered the diagnosis of coronary disease in two. Each of these disagreements was resolved by consensus.

Fifty studies were interpreted a second time in a blinded fashion by the same observer. The interpretations were identical in 45 cases. In three there was a difference in assessment of vessel involvement, and in two the diagnosis of coronary disease was changed.

Overall sensitivity and specificity for coronary artery disease (Table I): Only 1 of 14 patients without significant coronary artery disease manifested abnormal perfusion during exercise. Thus, the specificity* of scintigraphy was 93 percent. Fifty-seven of the 64 patients with coronary disease had an abnormal exercise scintigram; therefore the sensitivity† of scintigraphy was 89 percent. These 57 patients included 84 percent (26 of 31) of patients with coronary artery disease without previous infarction (Group 1) and 94 percent (31 of 33) of those with infarction (Group 2). This higher sensitivity level in patients in Group 2 was not statistically significant.

Scintigraphic abnormalities were present at rest or were substantially unchanged after time was allowed for redistribution only in the patients with prior infarction (Group II). Of the 31 patients in this group with a positive scintigram, 27 had resting perfusion defects or defects showing no redistribution. Seventeen of these also had exercise-induced defects and an additional four patients in Group 2 had perfusion abnormalities only with exercise. Thus, a total of 21 of 33 or 64 percent of the patients with possible prior infarction had exercise-induced abnormalities.

The negative studies among the patients in Group 1 occurred in two patients with one vessel disease, two patients with two vessel disease and one patient with three vessel disease. None of these had a stenosis greater than 90 percent. Neither of the two patients from Group 2 with normal studies had Q waves. One had a single 70 percent stenosis, and the other had a totally occluded right coronary artery with excellent collateralization from the patent left system. In only one patient could a false negative study be attributed to inadequate exercise; the other patients either achieved 85 percent of maximal heart rate, had angina pectoris or manifested ischemic electrocardiographic changes during exercise.

* Specificity = True positive/(True positive + False positive) × 100.

† Sensitivity = True positive/(True positive + False negative) × 100.

TABLE II

Comparison of Scintigraphic Prediction of Vessel Involvement With Arteriographic Results

Arteriographic Findings	Scintigraphic Interpretation			
	0 VD	1 VD	2 VD	3 VD
0 VD	**13***	1	0	0
1 VD	4	**7**	4	0
2 VD	2	6	**7**	0
3 VD	1	6	20	**7**

* Boldface numbers indicate the number of patients in whom the extent of coronary disease was correctly predicted (34 of 78 including patients without significant disease, 21 of 64 of those with disease).
VD = vessel disease.

Scintigraphic assessment of vessel involvement (Tables I to IV): In both the group with and the group without prior infarction, the majority of involved vessels were detected (43 of 73 [59 percent] and 55 of 74 [74 percent], respectively) in the exercise scintigrams (Table I). The sensitivity with which vessel involvement was diagnosed was not affected by the extent of coronary disease (that is, the number of vessels diseased) in a given patient because approximately two of three of the obstructed arteries resulted in corresponding areas of decreased perfusion in patients with one, two or three vessel disease (11 of 15, 20 of 30 and 67 of 102, respectively).

Table II compares the scintigraphic assessment of vessel involvement with coronary arteriographic findings. The majority of diseased vessels in the patients with coronary disease were detected, but the precise number of vessels involved was correctly recognized in only 21 of 64 patients—8 of 31 in Group 1 and 13 of 33 in Group 2. Figure 2 illustrates scintigrams that,

TABLE III

Sensitivity of Scintigraphy in Relation to Vessel Involved

	Proportion of Stenosed Vessels With Corresponding Scintigraphic Defects			
	Right	LAD	LCx	All Vessels
All patients with CAD	36/49 (73%)	42/54 (78%)	20/44 (45%)	98/147 (67%)
No infarct	13/22 (59%)	20/28 (71%)	10/23 (43%)	43/73 (59%)
Previous infarct	23/27 (85%)	22/26 (95%)	10/21 (48%)	55/74 (74%)
Normal Tl-201 at rest	7/11 (64%)	7/11 (64%)	3/14 (21%)	17/36 (47%)

CAD = coronary artery disease; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery.

although positive, did not correctly demonstrate the existence of disease.

The sensitivity of myocardial perfusion scintigraphy in diagnosing disease of each of the three major coronary arteries is shown in Table III. Although abnormal perfusion was detected in the distribution of most of the diseased right and left anterior descending coronary arteries (36 of 49 [73 percent] and 42 of 54 [78 percent], respectively), significantly fewer (19 of 44 [43 percent], $P < 0.001$) left circumflex coronary arterial lesions were recognized. This difference was apparent in patients in both Groups 1 and 2.

The severity of coronary arterial stenosis appeared to be the major determinant of the scintigraphic findings (Table IV). Perfusion was abnormal in the distribution of 80 percent (78 of 98) of vessels with severe (more than 90 percent) stenosis, but in only 39 percent (19 of 49) of those with less severe (70 to 90 percent obstruction ($P < 0.01$). This difference was apparent both in patients with and in those without infarction. The likelihood of a moderate (70 to 90 percent) stenosis resulting in a recognizable perfusion defect in a given patient was not influenced by the presence or absence of accompanying more severe lesions (5 of 14 without, 14 of 35 with). The scintigrams in Figure 2, from a patient with significant two vessel disease, show decreased perfusion only in the distribution of the more severely stenosed vessel.

Perfusion was thought to be abnormal in the distribution of only 8.5 percent (4 of 47) of vessels without

TABLE IV

Sensitivity of Scintigraphy in Relation to Severity of Stenosis*

	Severity of Coronary Stenosis		
	<70% Stenosis	70–90% Stenosis	>90% Stenosis
All patients with CAD	4/47 (9%)	19/49 (39%)	78/98 (80%)
No infarct	1/20 (5%)	10/29 (34%)	32/44 (73%)
Previous infarct	3/27 (11%)	9/20 (45%)	46/54 (85%)
Normal scintigram at rest	2/26 (8%)	7/14 (21%)	14/22 (64%)

* Data indicate the proportion of diseased vessels with corresponding scintigraphic defects.
CAD = coronary artery disease.

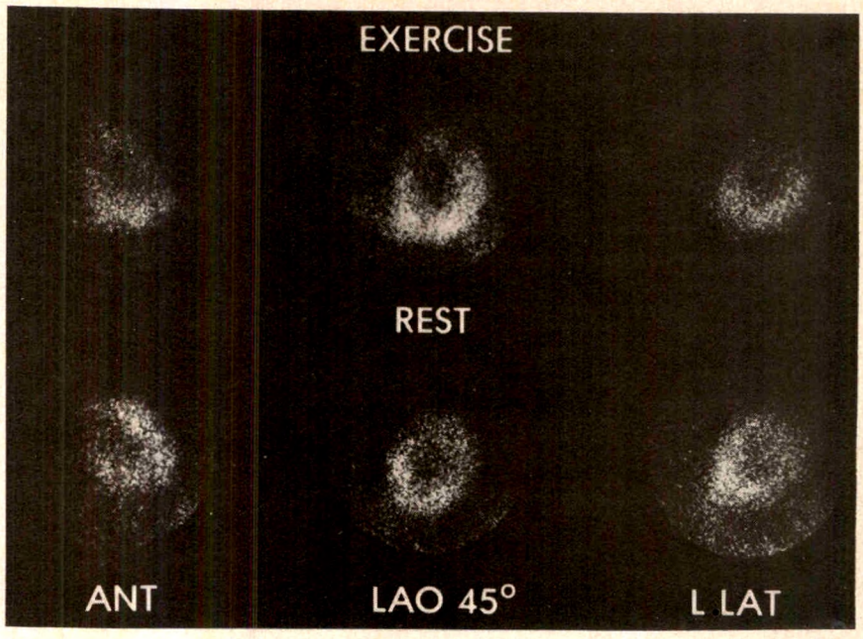

FIGURE 2. Scintigrams from a patient with more than 90 percent narrowing of the left anterior descending coronary artery and a 75 percent stenosis of the right coronary artery. The exercise scintigrams **(top)** show decreased perfusion of the anterior wall (anterior [ANT] and left lateral [LLAT] projections) but normal inferior wall thallium uptake. The study at rest **(bottom)** was normal. LAO = left anterior oblique.

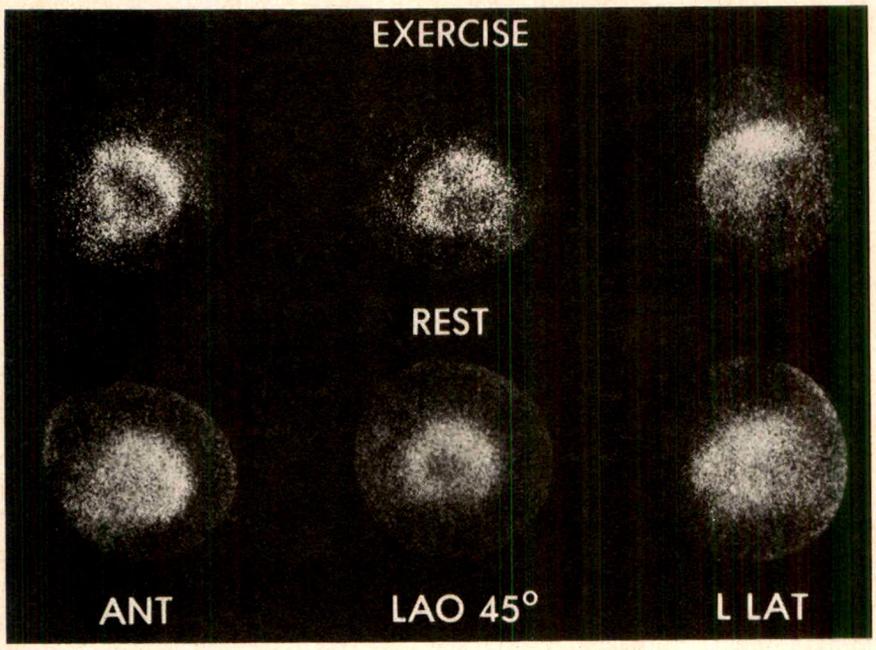

FIGURE 3. Scintigrams from a patient with a prior inferior myocardial infarction. A corresponding area of decreased perfusion is present in the scintigrams obtained at rest **(bottom)** (seen best in the left anterior oblique [LAO] view). During exercise, this defect became more prominent and is visible in all three projections. In addition, the images reveal abnormal perfusion of the posterior wall and apex during stress. ANT = anterior; LLAT = left lateral.

significant lesions in the 64 patients with coronary artery disease. Thus, even among these patients, the specificity of a regional abnormality as an indicator of significant disease of the corresponding vessel exceeded 90 percent.

Effect of previous myocardial infarction on overall and regional sensitivity of perfusion scintigraphy (Tables I, III and IV): As noted earlier, exercise scintigrams were more likely to be positive in patients with a previous myocardial infarction. When the results are examined by vessel distribution, this increased sensitivity in the group with infarction was present irrespective of the extent (Table I), localization (Table III), or severity (Table IV) of coronary artery disease. However, when only those regions that had normal perfusion at rest or showed significant redistribution in 3 to 4 hours were considered, the vessel by vessel and region by region sensitivity of the perfusion scintigrams was similar in the groups with and without infarction. Thus, 47 percent of diseased vessels in noninfarcted regions were detected in patients in Group 2, compared with 59 percent of such vessels in patients in Group 1. Similarly 21 and 64 percent, respectively, of moderately and severely obstructed vessels serving regions normally perfused at rest in the patients with infarction were detected, whereas 34 and 73 percent of such regions were detected in patients without infarction. Figure 3 shows the scintigrams obtained during exercise and at rest from a patient with a previous infarction who also manifested exercise-induced ischemia.

Discussion

Historical background: Although several methods are available to measure myocardial perfusion and coronary arterial blood flow, most require catheterization of either the coronary sinus or coronary arteries and therefore have limited clinical utility.[11] Potassium and its analogs, cesium, rubidium and thallium are actively concentrated in normal cardiac muscle. Thus, radioisotopes of these ions can be used to image the heart after peripheral injection.[1–8,12] Areas of old or recent myocardial infarction manifest reduced radionuclide uptake after injection of these agents at rest. When the radionuclides are injected during exercise, other regions with jeopardized circulation also display relatively diminished radioisotope uptake.

Thallium-201, because of its low energy of emission and high degree of concentration in myocardium, appears to be the agent best suited for cardiac imaging.[13–15] Several groups have examined the diagnostic accuracy of exercise myocardial scintigraphy using thallium-201. They have reported sensitivity levels of 75 to 89 percent and specificity levels of 89 to 100 percent.[1–4]

However, the technique of myocardial scintigraphy only provides data concerning relative myocardial perfusion. Thus, the perfusion of one myocardial region can be evaluated only in relation to other regions in the same patient. A recent experimental study suggested that a twofold difference in regional blood flow must be present before evidence of diminished perfusion is apparent.[16] As a result, patients with widespread disease of all three major coronary arteries might have false negative scintigrams because of a generalized reduction in blood flow.[1,4] Patients with previous myocardial infarction and critical lesions in more than one vessel theoretically might appear to have normal perfusion of regions that are, in fact, jeopardized. Most previous reports have not specifically addressed the questions of how the extent and severity of coronary disease and the presence of areas of infarction affect the scintigraphic findings.

Overall accuracy of thallium-201 scintigraphy: The diagnostic sensitivity of exercise thallium-201 scintigraphy in our patients was similar to or slightly greater than that previously reported.[1–4] The small differences may reflect variations in patient population. The high specificity of scintigraphy in our study (93 percent) is also consistent with previous reports.

Factors affecting regional sensitivity: In the patients with coronary artery disease, scintigraphy remained highly specific in diagnosing vessel involvement, classifying only 4 of 47 vessels that did not appear jeopardized anatomically as having abnormal perfusion. The overall sensitivity of scintigraphy in recognizing involved vessels was somewhat lower, 67 percent. On further analysis, several factors were found to affect significantly the sensitivity with which vessel involvement was detected.

The identity of the obstructed vessel was important, in that disease of the left circumflex coronary artery and corresponding abnormalities of the posterior wall were recognized less frequently than those of other vessels and regions. The 45, 73 and 78 percent sensitivity levels with which circumflex, right and left anterior descending coronary artery disease, respectively, were detected in our series were quite similar to the 49, 79 and 84 percent sensitivity levels previously reported for these vessels by Lenaers et al.[17]

The sensitivity with which jeopardized vessels were detected was not appreciably influenced by the extent of coronary artery disease. Thus, scintigraphy has similar regional sensitivity in patients with one vessel and multivessel involvement. The greater overall sensitivity of the technique in patients with multivessel disease merely reflects the greater number of regions in jeopardy. Thus, a homogeneous reduction in perfusion in patients with widespread disease appears to be very uncommon. In fact, our results indicate that patients with three vessel disease are those most likely to have abnormal scintigrams. Scintigraphy correctly predicted the precise number of arteries involved by arteriographic criteria in only a minority of patients. However, the regions that were abnormal may well be those most susceptible to ischemia.

The most important factor affecting the regional sensitivity of scintigraphy was the severity of the corresponding stenosis. Although almost 80 percent of the vessels with severe lesions (more than 90 percent stenosis) had corresponding perfusion defects during exercise, only 39 percent of the vessels with moderate (70 to 90 percent) narrowing were detected. This low frequency with which the moderate stenoses were associated with recognizable perfusion defects is somewhat surprising. Gould et al.[18] demonstrated that even less severe stenoses impair blood flow under conditions, such as exercise, that usually diminish coronary vascular resistance. One possible explanation, in view of the relative nature of the scintigraphic evaluation of perfusion, is that the less marked reduction of isotope uptake produced by these lesions is not apparent in relation to other more severe abnormalities. Alternatively, perhaps at the level of exercise usually achieved by patients with ischemic heart disease, even during symptom-limited testing, relative blood flow is not sufficiently reduced by such moderate lesions to produce apparent scintigraphic defects. Quantitative analysis of the scintigrams[19] or the use of the tomographic method recently described by Vogel et al.[20] may allow the detection of regions with less severe decreases of flow.

Effect of previous myocardial infarction: Because myocardial perfusion is reduced in both ischemic and infarcted myocardium, it seems likely that scintigraphy might prove more sensitive in patients with previous infarction. Because 50 percent or more of the patients with coronary artery disease in most studies of myocardial perfusion scintigraphy have had infarction, this point deserves further consideration. Indeed, our findings indicate that the sensitivity level was extremely high (94 percent) in patients with prior infarction but was also good (84 percent) in those without evidence of infarction.

Similarly, vessel by vessel sensitivity was higher in patients with infarcts. Of particular note is that the greater incidence of perfusion defects occurred in the regions with imaging abnormalities at rest or after redistribution, that is, the infarcted areas. The sensitivity of thallium-201 scintigraphy in the remaining jeopardized regions in these patients was quite similar to that in patients without infarction.

Limitations: Several methodologic limitations of our study deserve emphasis. The interpretation of coronary arteriograms is subject to considerable interobserver variability and may also sometimes be inaccurate when compared with postmortem anatomic findings.[21–23] Another potential explanation for discrepancies between the scintigraphic and arteriographic findings is the role of collateral blood flow. However, the adequacy of collateral circulation is extremely difficult to assess angiographically and was not considered in this present study. The third difficulty in relating the arteriographic findings to the scintigrams is the assumptions made concerning the regional distribution of the coronary arteries. Although care was taken to consider vessel dominance and the location of lesions, it is likely that these assumptions were not appropriate in some patients.

Experimental studies have demonstrated that small areas of decreased perfusion may not be detected with current scintigraphic techniques.[24] The sensitivity of exercise scintigraphy is clearly dependent on the level of exercise achieved and is greatly reduced at low levels of stress.[25] No attempt was made to exclude patients on the basis of their exercise performance because all tests were symptom-limited. As a result, our findings should be applicable to most patients undergoing such testing. The interpretation of the thallium-201 scintigrams is highly subjective, and this may explain the differences in the results reported by various centers.[25,26] Nonetheless, intraobserver reproducibility of interpretation was high and interobserver variability was relatively low in our study.

Lastly, the division of patients into groups based on evidence of previous infarction must be considered an approximation because the occurrence of electrocar-

diographically and symptomatically silent infarction is well known.

Clinical implications: Our findings reveal several advantages and certain limitations of thallium-201 myocardial perfusion scintigraphy. This technique is highly specific for coronary artery disease. Not only are abnormal studies uncommon in patients without significant stenoses, but regional abnormalities are rare except in the distribution of stenosed vessels. Scintigraphy is also quite sensitive, even in patients without previous infarction. Areas of diminished perfusion most frequently correspond to the vessels that are critically obstructed (more than 90 percent). When analyzed region by region, the sensitivity is not diminished by the presence of infarction or more severe stenoses involving other regions in the same patients. The majority of jeopardized regions will be detected, even in patients with multivessel disease.

It is also clear that in most patients some jeopardized regions will not be detected. In particular, lesions of the left circumflex coronary artery and those that are less severe are more often missed. As a result, thallium-201 scintigraphy does not allow precise quantitation of the number of vessels involved and is therefore less reliable in estimating the anatomic extent of coronary disease than in diagnosing its presence.

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Mechanism of Ventricular Fibrillation in Man

Observations Based on Electrode Catheter Recordings

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Observations are reported on the initiation and spontaneous termination of ventricular fibrillation in man using endocardial electrode catheter recordings. The report is based on 16 patients in whom ventricular fibrillation developed during electrophysiologic study. In 11 patients ventricular fibrillation was initiated by programmed ventricular stimulation and in 5 patients ventricular fibrillation occurred spontaneously. In each patient two to five simultaneous ventricular electrograms were recorded at the onset or termination, or both, of ventricular fibrillation. In most patients ventricular fibrillation began as a rapid and accelerating ventricular rhythm in which local electrograms remained discrete and with progressively shortening coupling intervals. Degeneration of local electrograms into fibrillatory activity occurred at random and at varying times. In four patients ventricular fibrillation developed spontaneously during sustained ventricular tachycardia. In these cases there was acceleration of the ventricular tachycardia before degeneration to ventricular fibrillation. Fragmentation and disorganization in local ventricular electrograms did not appear to spread between contiguous areas, but occurred randomly in widely separated areas. In six patients ventricular fibrillation spontaneously converted to sinus rhythm. In four of these cases spontaneous conversion was preceded by sequential reorganization of the electrograms and a tendency toward increasing interelectrographic intervals. These observations are compatible with the multiple wavelet (reentrant) theory of ventricular fibrillation.

The mechanism of ventricular fibrillation induced by acute ischemia or by a single ventricular stimulus of sufficient strength and duration has been considered by most investigators[1–6] to result from multiple reentrant wavelets creating sustained rapid and irregular excitation of the heart. However, some investigators[7,8] maintain that one or more rapidly firing foci can initiate and maintain ventricular fibrillation under experimental conditions. This report details our observations on the initiation (spontaneous or induced) and spontaneous termination of ventricular fibrillation in human beings using endocardial electrode catheter recordings.

Methods

Patients: Sixteen of 350 consecutively studied patients in whom ventricular fibrillation developed during electrophysiologic study form the basis of this report (Table I). In 11 patients ventricular fibrillation was induced by programmed ventricular stimulation and in 5 patients it occurred spontaneously either by degeneration from ventricular tachycardia (4 patients) or from spontaneous ventricular depolarizations (1 patient) (Table II). In each instance the electrophysiologic study was undertaken to evaluate documented or suspected ventricular tachycardia or ventricular fibrillation after written informed consent was obtained. There were 11 men and 5 women ranging in age from 18 to 73 years (Table I). Thirteen patients had a history of documented syncope or cardiac

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TABLE I

Clinical Data

Case no.	Age (yr) & Sex	Cardiac Diagnosis	ECG	History of Syncope or Cardiac Arrest	Spontaneously Documented Arrhythmias
1	73F	HCVD, ASHD	LVH	Yes	VF, VPDs
2	67M	NHD	Normal	Yes	VF, VT
3	54F	ASHD	NTMI	Yes	VPDs, VT, SB
4	24M	CM	IVCD	Yes	VF, VT, AF1, SVT
5	52M	ASHD	ASMI	Yes	VF, VT
6	53F	RHD, ASHD	ASMI, RBBB	Yes	VF, VT
7	72F	ASHD	LBBB, 1°AVB	Yes	VF, VPDs
8	18M	NHD	Normal	Yes	VT
9	67F	NHD	RBBB, LAH 1°AVB	No*	None
10	64M	ASHD	AMI, LAH, 1°AVB	Yes	VF, VT
11	46M	NHD	Normal	No*	SB
12	62M	ASHD	ASMI	Yes	VF, VT
13	66M	ASHD	ASMI	Yes	VF, VT
14	52M	ASHD, HCVD	LVH, IVCD	Yes	VF, VT
15	52M	RHD	AF, marked by prolonged Q-T (0.70 sec)	Yes	VF, VT
16	55M	NHD	Normal	No*	VF

* Recurrent near-syncopal episodes.

AF = atrial fibrillation; AF1 = atrial flutter; ASHD = atherosclerotic heart disease; ASMI = anteroseptal myocardial infarction; AVB = atrioventricular block; CM = cardiomyopathy; ECG = electrocardiogram; IVCD = intraventricular conduction defect; HCVD = hypertensive cardiovascular disease; LAH = left anterior hemiblock; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; NHD = no heart disease; NTMI = nontransmural myocardial infarction; RBBB = right bundle branch block; RHD = rheumatic heart disease; SB = sinus bradycardia; SVT = supraventricular tachycardia; VF = ventricular fibrillation; VPDs = ventricular premature depolarizations; VT = ventricular tachycardia.

arrest, or both; each of these had documented ventricular tachycardia or ventricular fibrillation. Three patients were studied because of near-syncopal episodes, one of whom had documented spontaneously converting ventricular fibrillation. Nine patients had atherosclerotic heart disease (two of whom also had hypertensive cardiovascular disease, and one of whom had concomitant rheumatic heart disease), one had cardiomyopathy, one had rheumatic heart disease and four had no heart disease.

Intracardiac recordings: Standard multipolar (two to six electrodes) electrode catheters (interelectrode distance 1 cm) were inserted percutaneously by way of the femoral or brachial veins and arteries (or both) and positioned within the heart under fluoroscopic guidance. In each patient two to five si-

TABLE II

Mode of Initiation and Termination of Ventricular Fibrillation

Case no.	Mode of Initiation: 2 VPDs	Mode of Initiation: Spontaneous VPD	Mode of Initiation: Spontaneous Degeneration From VT	Mode of Termination: Spontaneous	Mode of Termination: DC Shock
1	+	...	...	+	...
2	+	...	...	...	+
3	+	...	...	...	+
4	+	...	...	...	+
5	+*	...	...	...	+
6	...	...	+†	...	+
7	+	...	...	+	+
8	+	...	...	+	...
9	+	...	...	+	...
10	+	...	...	...	+
11	+	...	...	...	+
12	...	...	+	...	+
13	...	...	+	...	+
14	...	...	+†	...	+
15	...	+	...	+	...
16	+	...	...	+	...

* Two ventricular premature depolarizations delivered during ventricular tachycardia.

† Ventricular fibrillation also induced by two ventricular premature depolarizations delivered during ventricular tachycardia.

DC = direct current; VPD = ventricular premature depolarization; VT = ventricular tachycardia.

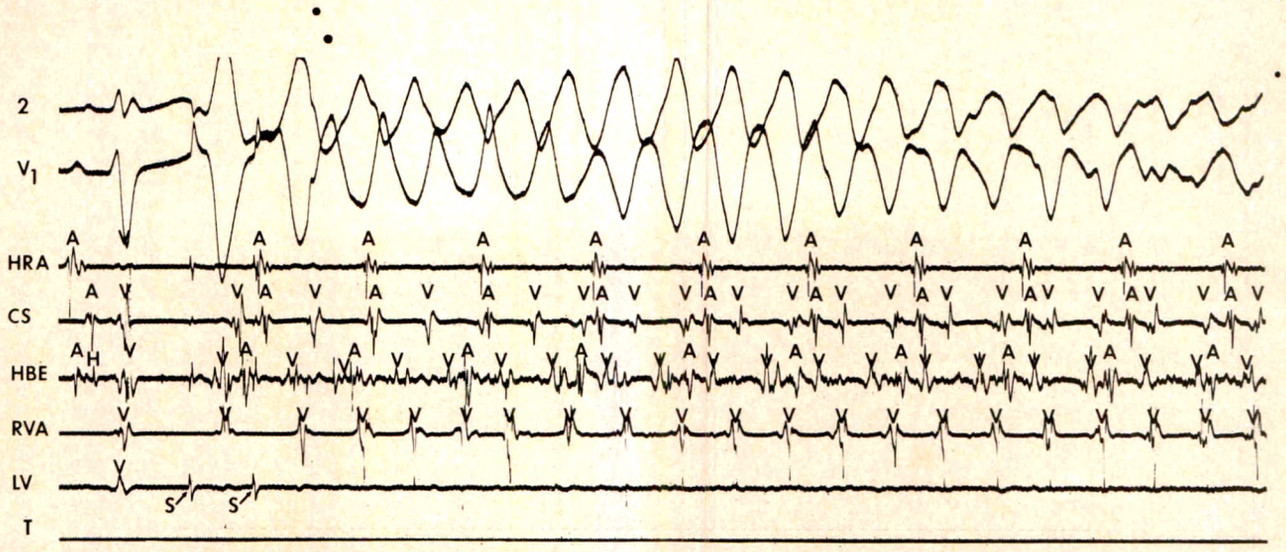

FIGURE 1. Case 8. Initiation of ventricular fibrillation by two ventricular extrastimuli during sinus rhythm. The panel is organized **from top to bottom** as electrocardiographic leads II (2) and V_1, electrograms from the high right atrium (HRA), coronary sinus (CS), atrioventricular junction at the His bundle recording site (HBE), right ventricular apex (RV) and left ventricular apex (LV), and time lines (T). After the first sinus complex two ventricular extrastimuli (S_1, **arrow**) delivered from the right ventricular outflow tract at coupling intervals of 280 and 240 msec, respectively, result in electrocardiographic ventricular fibrillation. The onset of ventricular fibrillation is associated with accelerating discrete ventricular electrograms in the coronary sinus and right ventricular apex while the His bundle and left ventricle demonstrate "local fibrillation." The electric activity in the left ventricle appears lower in amplitude and irregularly undulating. During fibrillation the ventricular electrograms from the right ventricular apex and coronary sinus remain regular and discrete.

multaneous ventricular electrograms were recorded at the onset or termination, or both, of ventricular fibrillation. These always included electrograms recorded at the atrioventricular (A-V) junction (His bundle electrogram) and right ventricular apex. In 12 patients a coronary sinus electrogram recording posterobasal left ventricular activity and in 11 patients one or two bipolar left ventricular electrograms obtained from catheters positioned in the left ventricle were obtained during ventricular fibrillation. All electrograms were filtered at 40 and 500 hertz and simultaneously displayed with two or three surface electrocardiograms. The data were recorded on a Honeywell 5600C tape recorder and later retrieved on photographic paper at speeds of 100 to 400 mm/sec. In patients whose ventricular fibrillation did not spontaneously convert to normal sinus rhythm, direct current shock was utilized to reestablish sinus rhythm as soon as loss of consciousness occurred. This ranged from 5 to 11 seconds.

Stimulation protocol: Stimulation was performed using a custom-designed programmable stimulator (Bloom Associates Inc., Narberth, Pennsylvania) with optically isolated constant current sources. Stimuli were 1 msec in duration and twice diastolic threshold, ranging from 0.6 to 2.5 milliamperes (ma). All equipment was isolated from the patients, and leakage current ranged from 2 to 6 μa.* The stimulation protocol included the introduction of single and double ventricular extrastimuli during sinus rhythm, ventricular pacing and ventricular tachycardia as previously reported.[9]

* Leakage current was measured by David Bradley at the Illinois Institute of Technology-Research Institute in Chicago. This was done using a 100 ohm 1 percent resistor in parallel with a 0.15 microfarad capacitor and a 10 ohm resistor connected between the grounded supply conductor and grounded in metal parts or ordinary patient connections of the stimulator. The voltage across the resistor was measured and current through it calculated. Measurements were made during various operating modes with a grounding conductor open or closed, with the line polarity normal or reversed, and with the neutral conductor closed.

Ventricular fibrillation was defined using standard electrocardiographic criteria as a rapid ventricular arrhythmia with irregular polymorphic complexes. The diagnosis of ventricular fibrillation based on surface electrocardiographic criteria did not take into account electrical activity recorded in local ventricular electrograms. Rapid, irregular and frequently continuous electrical activity observed in an intracardiac electrogram was called "local fibrillation," although the exact mechanisms of such activity is not yet established.

Results

Mode of initiation of ventricular fibrillation: In 11 patients ventricular fibrillation was initiated by the introduction of two ventricular premature depolarizations during ventricular pacing (9 patients) or sinus rhythm (two patients) (Fig. 1 and 2, Table II). In nine patients these depolarizations were delivered from the right ventricle and in two patients from the left ventricle. Left ventricular stimulation was performed only after right ventricular stimulation had failed to initiate a tachyarrhythmia. In each patient in whom ventricular fibrillation was initiated by double ventricular premature stimulation, single ventricular premature stimuli scanning diastole had failed to induce the arrhythmia. Although "local fibrillation" occurred in at least one intracardiac recording immediately after the second stimulus in three patients (Fig. 1), one or more discrete repetitive ventricular complexes were observed more commonly (in 7 of 10 patients) before fragmentation occurred in any individual intracardiac recording (Fig. 2). In no instance did all of the intracardiac ventricular electrograms degenerate into local fibrillation simultaneously. Occasionally two ventricular electrograms degenerated simultaneously but the electrograms from

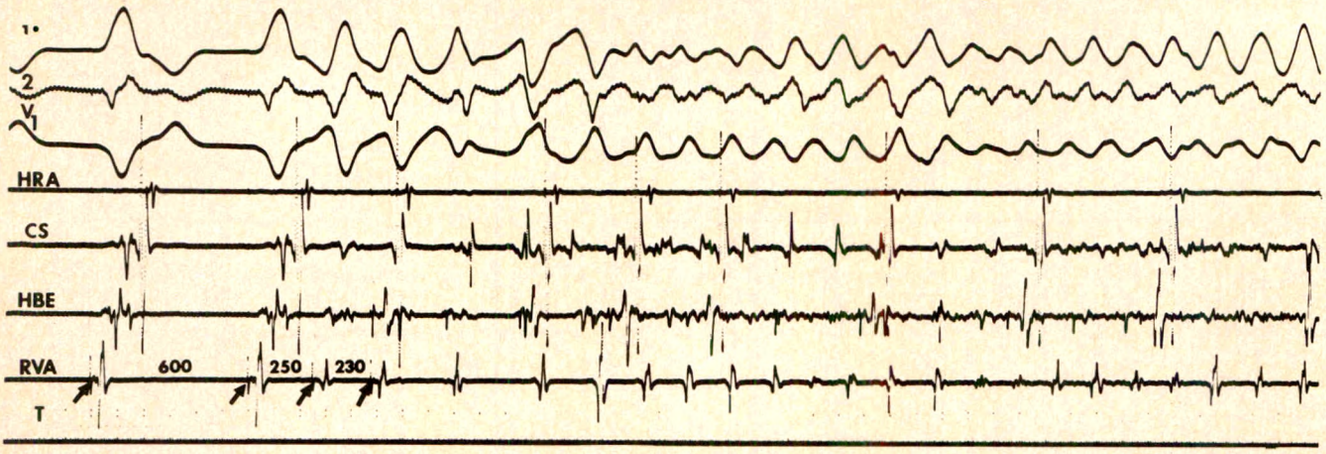

FIGURE 2. Case 16. Initiation of ventricular fibrillation by two ventricular extrastimuli during ventricular pacing. The recordings are organized from **top to bottom** as electrocardiographic leads I (1), II (2) and V_1 and intracardiac electrograms from the high right atrium (HRA), coronary sinus (CS), His bundle region (HBE) and right ventricular apex (RVA), and time lines (T). During a basic ventricular drive of 600 msec (S_1, **arrow**) two ventricular extrastimuli delivered from the right ventricular apex initiate ventricular fibrillation. The onset of ventricular fibrillation is associated with progressive acceleration and fragmentation of the intracardiac ventricular electrograms, which occurs initially in the His bundle, which is distant from the site of stimulation. Fractionation occurs last in the right ventricular apex, which was the site of stimulation.

the remaining areas of the ventricle degenerated at various periods of time after the fragmentation in the electrogram first showing "local fibrillation." Furthermore, there was no pattern in which local ventricular fibrillation developed; that is, fibrillation did not appear to spread from the right to the left ventricle or vice versa.

In each case in which double stimuli produced ventricular fibrillation, the second ventricular extrastimulus was introduced at a shorter coupling interval than the first extrastimulus, and in the patients who had one or more additional spontaneous ventricular responses before degeneration, the coupling intervals of those ventricular complexes shortened before degeneration in any individual electrogram (Fig. 2). Thus, at the onset of ventricular fibrillation initiated by ventricular premature depolarizations, there was an acceleration of ventricular responses in any local ventricular electrogram that preceded fragmentation of that electrogram. This acceleration was coincident with an acceleration of ventricular complexes in the surface electrocardiogram before appearance of electrocardiographic ven-

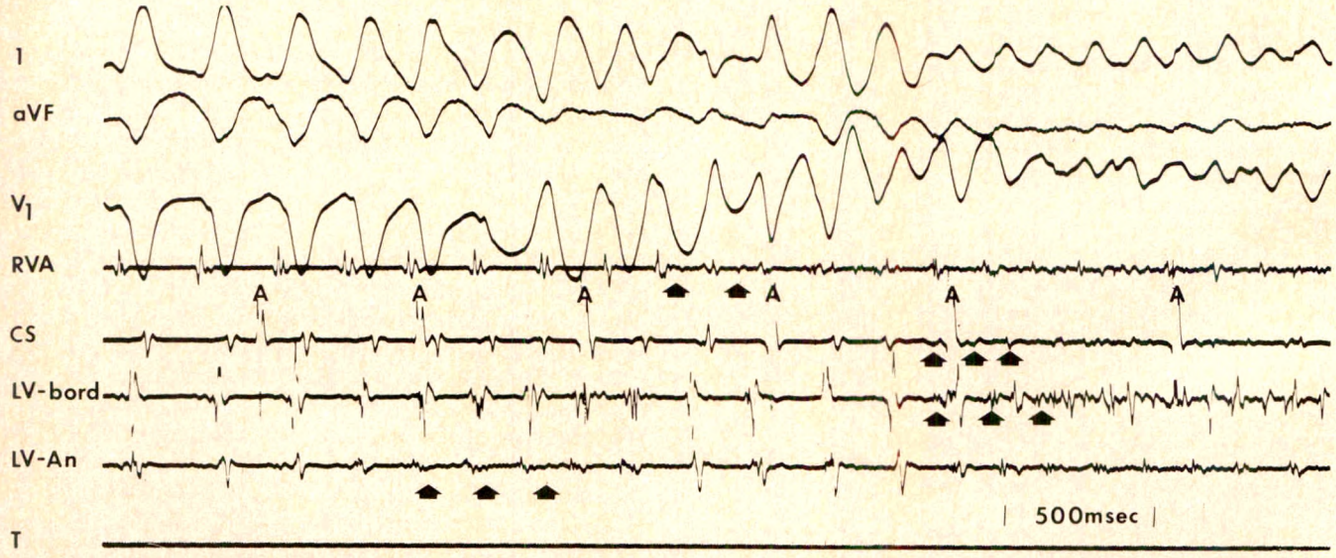

FIGURE 3. Case 12. Spontaneous degeneration of ventricular tachycardia to ventricular fibrillation. The panel is arranged **from top to bottom** as electrocardiographic leads I (1), aVF and V_1, and electrograms from the right ventricular apex (RVA), coronary sinus (CS), border of an apical left ventricular aneurysm (LV-bord) and from within the aneurysm (LV-An), and time lines (T). Before the development of ventricular fibrillation (**right**) there is sudden acceleration of ventricular tachycardia with the development of pleomorphic forms. The intracardiac electrograms also demonstrate acceleration with the noncontiguous development of fractionation of each electrogram (**arrows**). The fractionation was initially transient in the left ventricular aneurysm but then became persistent. A.

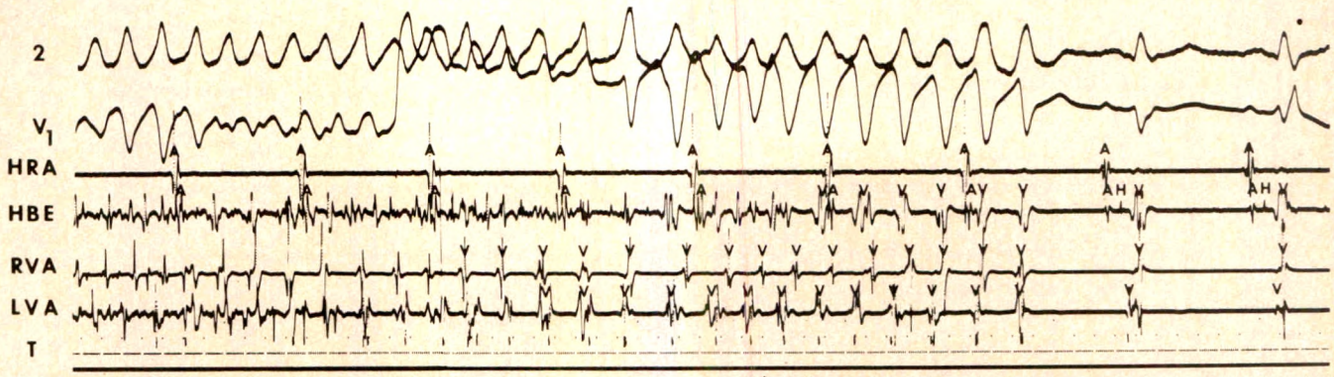

FIGURE 4. Case 9. Spontaneous termination of ventricular fibrillation by gradual reorganization. The panel is organized **from top to bottom** as electrocardiographic leads II (2) and V_1 and electrograms from the high right atrium (HRA), His bundle region (HBE), right ventricular apex (RVA) and left ventricular apex (LVA), and time lines (T). During ventricular fibrillation reorganization of the right ventricular apex precedes reorganization of the left ventricular apex and His bundle. When all three electrograms become discrete and synchronous, fibrillation ceases and sinus rhythm ensues.

tricular fibrillation (Fig. 2). An example of this phenomenon is shown in Figure 2. Acceleration of electrograms from the coronary sinus, His bundle region and right ventricular apex preceded degeneration to local fibrillation. Frequently during acceleration of electrograms before total disorganization, splitting of the original electrogram into two or more discrete components was observed.

In four patients ventricular fibrillation developed spontaneously during sustained ventricular tachycardia (Fig. 3, Table II). In these cases acceleration of the ventricular tachycardia occurred before degeneration to ventricular fibrillation. The fragmentation and disorganization in local ventricular electrograms did not appear to spread between contiguous areas but occurred randomly in widely separated areas. This phenomenon is demonstrated in Figure 3, in which early (transient) disorganization of the electrograms in the left ventricular aneurysm precede degeneration at the right ventricular apex, and finally electrograms at the posterior basal area of the left ventricle and border of the aneurysm degenerate to local fibrillatory activity. Only when all intracardiac recordings show fibrillation simultaneously did the surface electrocardiogram become totally chaotic and amorphous (see later).

In one patient with a procainamide-induced long Q-T interval (0.65 to 0.70 second), spontaneous self-terminating episodes of multiform ventricular tachycardia (torsades de pointe) or fibrillation occurred. Episodes lasted from 2 to 20 seconds. The initiating ventricular premature depolarization of the prolonged episode (20 seconds) of ventricular fibrillation had a coupling interval of 480 msec that coincided with the peak of the T wave. Brief episodes (2 to 5 seconds) of nonsustained "torsades de pointe" occurred when premature ventricular depolarization occurred at coupling intervals greater than 600 msec.

Maintenance and termination of ventricular fibrillation: In six cases ventricular fibrillation spontaneously converted to sinus rhythm. In four cases spontaneous termination was preceded by reorganization of the electrograms with the appearance of discrete recordings and increasing interelectrographic intervals (Fig. 4). After this change synchronization of the ventricular electrograms occurred and then abrupt termination was observed.

In two cases (Cases 7 and 15) multiple episodes of short-lived ventricular fibrillation spontaneously terminated when the major deflection in the intracardiac recordings occurred with abrupt synchronization of the ventricular electrograms. In neither case did a gradual reorganization of intracardiac electrograms precede termination. This is demonstrated in Figure 5 (Case 7), in which spontaneous termination of ventricular fibrillation is associated with sudden (one complex) organization and synchronization of electrograms from the coronary sinus, His bundle region and right ventricular apex.

In one patient (Case 10) ventricular fibrillation changed to a multiform ventricular flutter, then rapid ventricular tachycardia, which was then terminated by rapid pacing. During ventricular fibrillation and polymorphic ventricular flutter in the surface electrocardiogram, only the local ventricular electrogram from the A-V junction showed continuous fractionated activity, whereas that of the right ventricular outflow tract showed intermittent fragmentation alternating with long periods of regular discrete electrograms (Fig. 6). The remaining recordings from both the left and the right ventricle demonstrated regular discrete electrograms at a cycle length of 180 msec. This rhythm abruptly changed to a slightly slower rhythm (cycle length, 220 msec) with a narrow QRS complex and a clear isoelectric baseline, which was associated with the sudden organization of the electrogram in the A-V junction to broad but discrete electric activity. The electrogram recorded from the right ventricular outflow tract also became more discrete. The ventricular tachyarrhythmia that ensued had a relatively narrow QRS complex (110 msec) and had its earliest site of activation recorded at the left ventricular apex. This rhythm, although rapid enough to be classified as ventricular flutter by rate alone, had clear isoelectric intervals between complexes and therefore probably

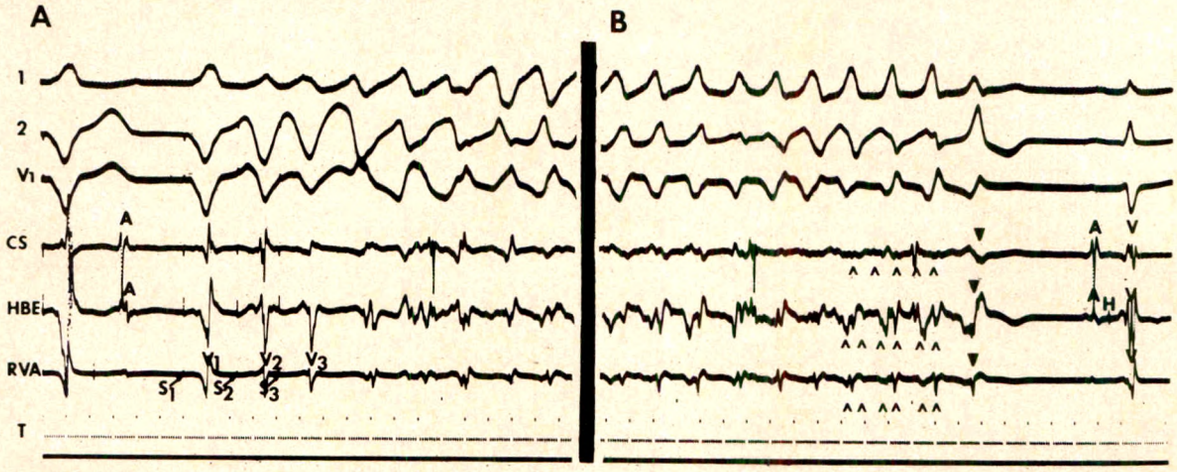

FIGURE 5. Case 7. Abrupt spontaneous conversion of ventricular fibrillation. The figure is arranged as in Figure 2. In **A**, ventricular fibrillation is initiated by two ventricular extrastimuli (S_2, S_3). Note that all intracardiac electrograms are fractionated. In **B**, spontaneous termination occurs when the chaotic electrograms (**open arrowheads**) suddenly coalesce and fuse into broad but discrete synchronous electrograms (**solid arrowheads**).

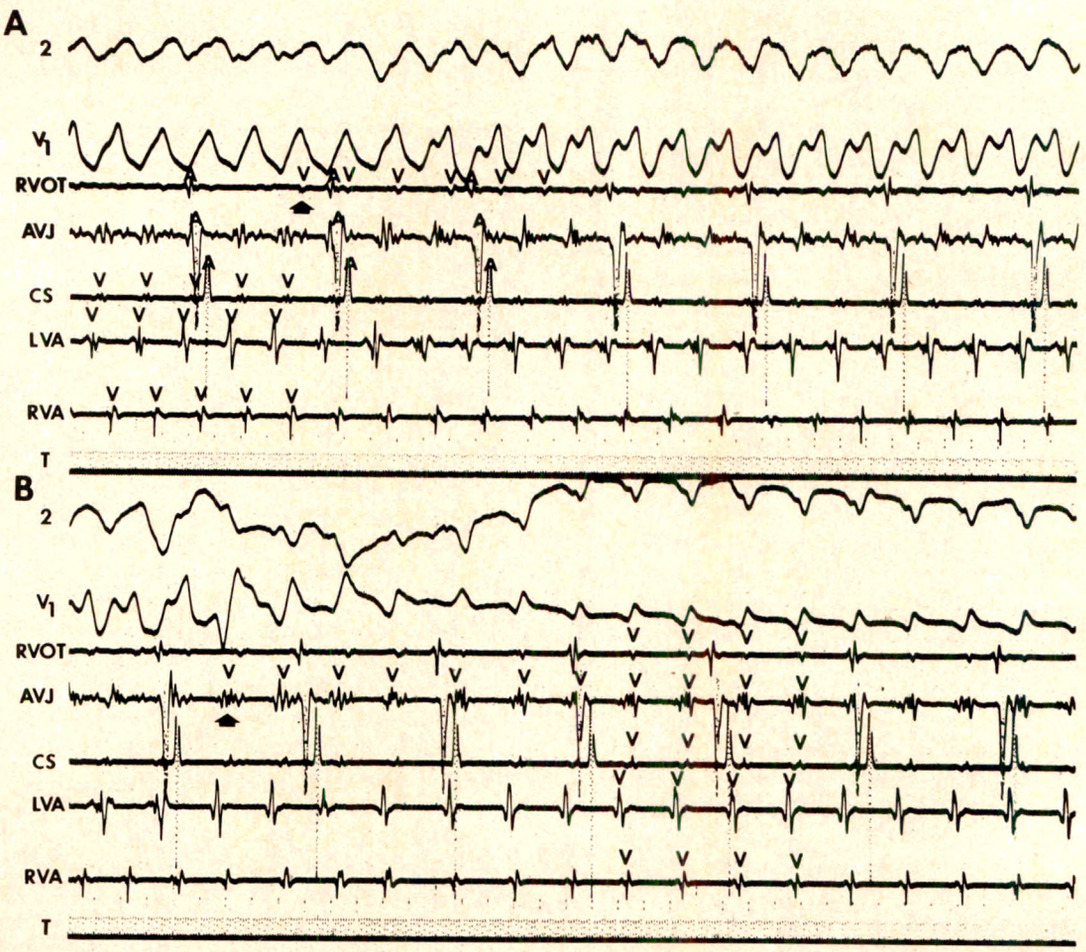

FIGURE 6. Case 13. Intracardiac recordings during transition from polymorphic ventricular flutter to ventricular tachycardia. In panels **A** and **B** surface leads II (2) and V_1 are shown with electrograms from the right ventricular outflow tract (RVOT) as recorded from the tip of the right atrial appendage, atrioventricular junction (AVJ), coronary sinus (CS), left ventricular apex (LV) and right ventricular apex (RVA). Panels **A** and **B** are continuous and show the conversion of polymorphic ventricular flutter to a narrow complex ventricular tachycardia with discrete isoelectric intervals (**panel B**). Initially the electrogram in the right ventricular outflow tract is fragmented and of low amplitude before regularizing (**broad arrow, panel A**). The electrogram from the atrioventricular junction remains continuously fragmented throughout **panel A** until just before transition to ventricular tachycardia, when it becomes organized and discrete, **panel B** (**arrow**). During polymorphic flutter, electrograms from the coronary sinus, right ventricular apex and left ventricular apex remain discrete despite fragmentation elsewhere. During ventricular tachycardia (**panel B, right**) all electrograms are discrete and regular. I = time lines.

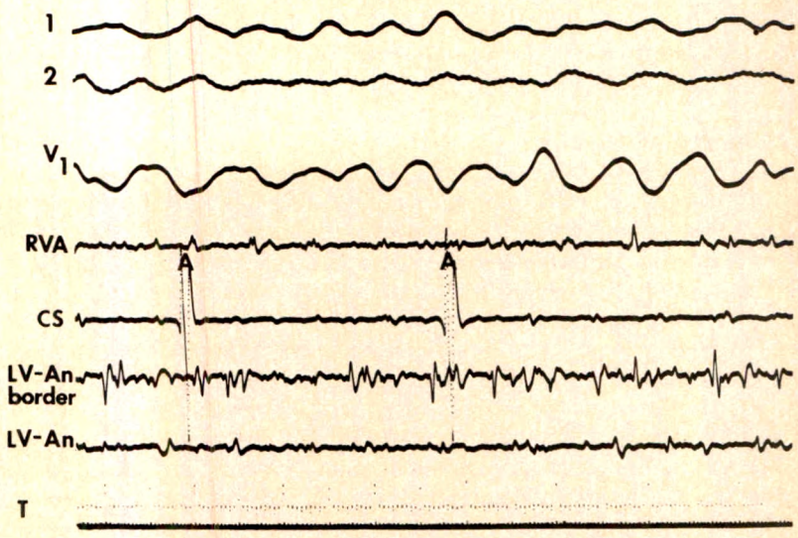

FIGURE 7. Case 12. Relation of intracardiac electrograms to QRS configuration during ventricular fibrillation. The figure is organized as in Figure 3. During ventricular fibrillation all ventricular electrograms show chaotic activity.

represented a rapid ventricular tachycardia. A burst (five stimuli) of rapid ventricular pacing at a cycle length of 200 msec terminated this arrhythmia.

In the remaining patients a direct current shock was required to terminate ventricular fibrillation. This was accomplished without neurologic or cardiac sequelae in all instances.

Relation of QRS configuration to local ventricular electrograms: In each case when all intraventricular electrograms demonstrated "local fibrillation," the QRS configuration was grossly irregular, disorganized and continually undulating (Fig. 7). However, similar QRS patterns were also associated with one or more intracardiac ventricular electrograms that were completely organized and regular, whereas others were completely disorganized (Fig. 1, 2 and 4). The development of "local ventricular fibrillation" was not irreversible, and frequently one or more ventricular electrograms demonstrated "local fibrillation," which alternated with more discrete electrograms (Fig. 2 and 3).

It was not possible to predict the nature of the activity in the intracardiac recordings by analysis of the QRS configuration. Although a totally disorganized QRS configuration was usually associated with a larger number of intraventricular electrograms demonstrating "local ventricular fibrillation," the number and type of fragmented electrograms at any point in time could not be predicted.

Discussion

Ventricular fibrillation is usually defined by its typical electrocardiographic manifestations, which have been considered to represent the result of chaotic, random and asynchronous electrical activation of the ventricles.[1–6] The mechanism of ventricular fibrillation—either multiple repetitive reentrant wavelets or rapid focal discharges—is not yet established in human beings. The use of intracardiac recording and programmed stimulation has allowed us to analyze the mechanisms of ventricular fibrillation in 16 patients and compare these findings with experimental models of ventricular fibrillation.

Mode of initiation of ventricular fibrillation: Our results suggest that the concept of a critically short coupling interval (R on T phenomenon) of single ventricular premature depolarizations under our experimental conditions does not seem to be a necessary factor for the development of ventricular fibrillation in the absence of acute ischemia for two reasons: (1) Ventricular fibrillation induced during programmed stimulation is rare, and (2) single ventricular extrastimuli scanning diastole to ventricular refractoriness at twice diastolic threshold failed to produce ventricular fibrillation in any of our patients in whom ventricular fibrillation developed.[10] In all instances of ventricular fibrillation induced by programmed stimulation two ventricular extrastimuli were required, and one or more additional repetitive ventricular responses were frequently observed before degeneration to ventricular fibrillation in both local ventricular electrograms and the surface electrocardiogram occurred. Moreover, the observation of ventricular fibrillation initiated by late spontaneous ventricular premature depolarizations in the setting of acute myocardial infarction in human patients or after acute coronary ligation in animals further supports the concept that the coupling interval of single ventricular premature depolarizations is not critical in the genesis of ventricular fibrillation.[11,12]

Recent human studies have shown that ventricular pacing shortens ventricular refractoriness[13] and ventricular stimulation has been shown to increase temporal dispersion of refractoriness and decrease ventricular fibrillation threshold in animals.[14] These data suggest that the observations at the onset of ventricular fibrillation are related to factors that produce inhomogeneity in ventricular activation and recovery and the shortening of ventricular refractoriness—the most important prerequisites for the development of ventricular fibrillation.

Our observations in man are consonant with these experimental studies because they demonstrate that at least two stimulated ventricular premature depolarizations of increasing prematurity usually followed by further acceleration of local ventricular electrograms were required to provide the substrate for degeneration into ventricular fibrillation. This suggests that the initial ventricular premature depolarization shortens ventricular refractoriness and increases the inhomogeneity of recovery so that the threshold for ventricular fibrillation was lowered for subsequent ventricular premature depolarizations. Second and additional ventricular premature depolarizations act as a group of accelerated responses with progressive shortening of refractoriness, increasing inhomogeneity of recovery until the appearance of fractionated electrograms at which time ventricular fibrillation ensues. This pattern was typical of those patients who had ventricular fibrillation in response to ventricular extrastimuli and are most consistent with reentry as the mechanism for fibrillation. These findings are analogous to those of Wiggers and co-workers,[1,2] Moe et al.[3] and Harris and Rojas,[4] who observed that a run of rapid impulses of increasing frequency preceded the development of fibrillation induced either by stimuli 10 to 30 msec in duration (5 to 40 ma) or acute ischemia.

A second mode of initiation of ventricular fibrillation resulted from ventricular tachycardia that underwent sudden acceleration and degeneration to a disorganized rhythm. This pattern is analogous to the type B pattern described by Watanabe and Dreifus[15] as well as by Harris and Rojas.[4] The ventricular fibrillation induced in this manner was usually preceded by a change in relation of electrograms to each other with progressive fragmentation in one or more areas until fibrillation ensued. In our patients fragmentation did not occur simultaneously in all areas and did not appear to spread from one focus of fibrillation to the remainder of the heart, but appeared to arise in different areas of the heart and then gradually envelop the entire heart. This differs from experimental ventricular fibrillation induced by either a strong current[3] or ischemia[4] during which the acceleration of responses and ventricular fibrillation begin at either the site of stimulation of the ischemic area and spread from there to the remainder of the heart. Furthermore, in the patients in whom ventricular fibrillation was initiated by double ventricular extrastimuli "local fibrillation" always appeared to occur initially distant to the site of stimulation, especially when stimulation was in the right ventricle.

However, the data do suggest that a generalized state of ventricular fibrillation throughout the heart results from independent areas degenerating into ventricular fibrillation that ultimately engulfs the remainder of the heart in the fibrillation process. This is to be distinguished from the spread of fibrillation from the initially fibrillating area to adjacent areas, the mechanism previously observed in experimental models.[3,4] The apparent requirement of shortened ventricular refractoriness, fractionation and desynchronization of local electrograms before the development of fibrillation is most consistent with the reentrant wavelet theory of its genesis.[16]

Maintenance and termination of ventricular fibrillation: Previous investigators have demonstrated that maintenance of ventricular fibrillation requires a large mass of tissue with an irregularly shortened refractory period and persistent areas of slow conduction and local block to allow continued reexcitation.[16–18] According to the wavelet theory of continued reexcitation,[16,17] the more wavelets present the less likely they would be to collide and extinguish the arrhythmia. Progressive block in large areas or marked lengthening of refractoriness caused by drugs or potassium chloride can result in progressive organization of these fragmented electrograms followed by termination of the arrhythmia.[1,2,5] In four of our six cases of spontaneous termination, a sequence occurred that is most compatible with the multiple microreentrant (wavelet) theory of ventricular fibrillation and suggests that maintenance of the arrhythmia is not dependent on a rapidly firing focus. Progressive organization results from inability of multiple areas to be reexcited sequentially, which therefore reduces the number of the wavelets that then can collide to extinguish the arrhythmia. Although large areas of fibrillation (electrograms from both the right and the left ventricle) were observed in four of the six patients who had spontaneous defibrillation, reorganization was observed before termination of the arrhythmia. Our observations suggest that the mass of muscle required to maintain fibrillation is dependent on the electrophysiologic properties of the heart; that is, a larger mass is required if conduction is not slow enough and refractoriness is not short enough to maintain reexcitation. Therefore, we believe that mass is a secondary prerequisite. In animal experiments in which the hearts are small, mass may play a more important role than it does in the larger, human heart.

Local electric activity during ventricular fibrillation: In many of our cases of ventricular fibrillation the surface electrocardiogram showed ventricular fibrillation only when one or two intracardiac electrograms manifested fibrillatory activity. This situation is analogous to atrial flutter-fibrillation in which parts of the atria demonstrate organized activity while other areas demonstrate localized fibrillation. An explanation of this phenomenon would be that those areas with more organized activity have longer refractory periods that prevent reexcitation despite slowed conduction, thereby preventing the formation of small wavelets. This would produce a slower, more organized pattern in these areas. Thus, the regular discrete activity in some areas could be the result of activation from isolated sites of fibrillation, whose rate would be determined by the local refractoriness.

Local continuous electric activity in a single intracardiac beat has also been described during reentrant ventricular tachycardia.[19–21] Although these recordings appear to show local fibrillation, many observations suggest that they do not. This continuous electric ac-

tivity could be reproducibly terminated by programmed ventricular stimulation, which would be very unlikely for true fibrillation. The continuous electric activity never spread beyond the single recording site, even when it was not confined by anatomic boundaries, such as a ventricular aneurysm. If the continuous electric activity was indeed local ventricular fibrillation, acceleration of the ventricular arrhythmia would be expected because the effective refractory period of the surrounding tissue was shorter than the cycle length of the tachycardia, and this property would be a major controlling factor of the cycle length of the tachycardia. It is thus more likely that continuous local electric activity in ventricular tachycardia represents a slow, irregular spread of an impulse over a single reentrant loop with abortive attempts to spread through multiple "physiologic dead end" pathways.[19,20,22,23]

Implications of study: Use of intracardiac recordings has allowed us to describe patterns in the development and termination of ventricular fibrillation. Although our observations are limited by the number of recording sites, they are most compatible with the multiple wavelet (reentrant) theory of ventricular fibrillation. The apparent dependence on refractoriness and fractionation of activity representing local block is most consistent with reentrant phenomena and argues against automaticity as the method for sustaining the arrhythmia. Our data cannot exclude the role of triggered automaticity as a cause for the early initiating complexes during spontaneous ventricular fibrillation, but in the chronically infarcted canine model these have also been shown to be most consistent with reentry.[19,20] Although the use of more catheters would be required to delineate more accurately the mechanisms responsible for initiation, maintenance and termination of ventricular fibrillation, it is unlikely that more than four or five catheters can be positioned without increasing risk to the patient. Intraoperative studies recording multiple simultaneous electrograms may provide the only method of analyzing in more detail the mechanisms of this arrhythmia in human beings.

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R on T or R on P Phenomenon? Relation to the Genesis of Ventricular Tachycardia

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Continuous electrocardiographic monitoring of 225 patients with acute myocardial infarction was performed during the initial 48 hours after admission. Two hundred twelve episodes of ventricular tachycardia occurred in 49 subjects, and 8 patients had primary ventricular fibrillation. Most cases of ventricular tachycardia were associated with late coupling of premature ventricular complexes. Of the 212 instances of ventricular tachycardia, 42 (20 percent) were initiated by a premature complex on the T wave (R on T) (R-R′/Q-T less than 1), and 93 (44 percent) had initiating premature complexes that occurred directly after onset of the sinus P wave (R on P). Of eight episodes of ventricular fibrillation, seven were initiated by a premature ventricular complex and in four of these there was associated R on T phenomenon. The influence of atrial contraction and myocardial stretch on reentry or ectopy is proposed as a possible explanation for the relatively high incidence rate of ventricular tachycardia observed after the onset of the sinus P wave.

Since first characterized by Smirk and Palmer,[1,2] premature ventricular complexes interrupting the antecedent T wave (R on T) have been considered ominous[3,4] and a phenomenon requiring aggressive pharmacologic intervention in the setting of acute myocardial infarction.[5] However, a recent compilation of data has challenged this concept.[6] During 1976, review of daily electrocardiographic monitoring strips from our coronary care unit revealed that ventricular tachycardia was frequently initiated by premature depolarizations that occurred immediately after the sinus P wave (R on P). These observations prompted a prospective study of the prevalence of this finding in subjects with documented myocardial infarction.

Methods

Selection of patients: Between October 1, 1977 and September 30, 1978, a total of 785 patients were admitted to the coronary care unit of our institution. From these 785 cases, we selected 225 with documented acute myocardial infarction. The criteria for myocardial infarction[7] included at least two of the following: (1) a history of sustained chest pain consistent with myocardial ischemia, (2) classic evolutionary electrocardiographic changes associated with the diagnosis, and (3) a rise in the serum level of specific cardiac enzymes. Subjects with the following findings were excluded from study: (1) pulmonary edema, (2) cardiogenic shock, (3) sinoatrial arrest or block, (4) atrial flutter or fibrillation, and (5) second or third degree atrioventricular (A-V) block. The study group represented consecutive patients who fulfilled criteria for infarction and did not have the aforementioned complications. Only three subjects had simultaneous atrial fibrillation and ventricular tachycardia. All patients were continuously monitored by telemetry for the first 48 hours after entry into the coronary care unit, and a review of recorded episodes of ventricular ectopic beats, tachycardia and fibrillation was performed independently by two physicians.

Ventricular tachycardia: Criteria for the diagnosis of ventricular tachycardia included (1) three or more abnormally wide (more than 0.12 second) QRS

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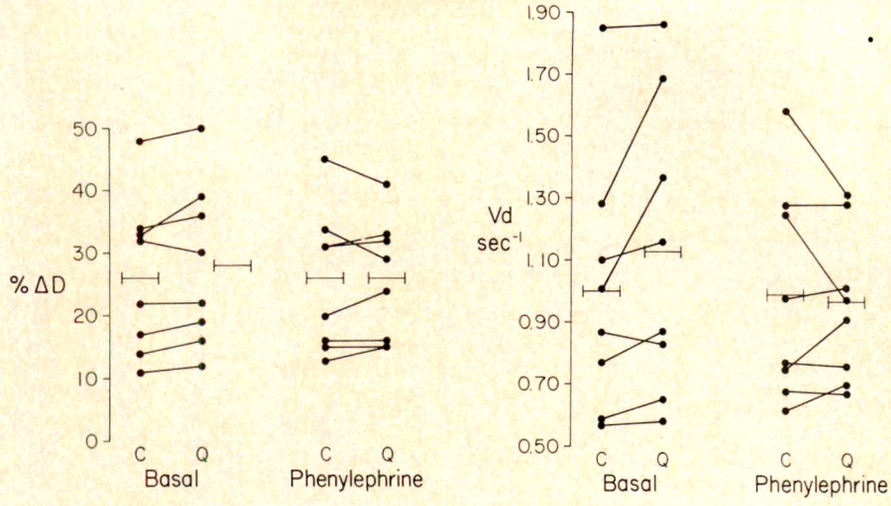

FIGURE 1. Left, percent left ventricular dimension shortening (%ΔD) (**ordinate**) is shown for each of the eight patients with cardiomyopathy receiving placebo (control, C) and after quinidine (Q) in the basal state and during infusion with phenylephrine. **Bars** represent the mean values. **Right,** normalized mean rate of left ventricular dimension shortening (Vd) (**ordinate**) is shown with use of the same format.

pharmacologic pressure loading at matched heart rate and blood pressure, left ventricular performance was not different with quinidine. Interestingly, the patients with cardiomyopathy did not exhibit any change in left ventricular function at any phase of the study while taking oral quinidine as compared with placebo. Thus, any direct myocardial depressant action of oral quinidine therapy seems to be so mild that no appreciable effect is demonstrable in patients with compromised cardiac function at rest or during acute pressure loading.

Echocardiography to assess left ventricular performance: M mode echocardiography can accurately estimate left ventricular performance in normal subjects and patients with symmetric left ventricular performance,[18–21] but is it sensitive enough to detect subtle changes in performance induced by drugs such as quinidine? Changes in left ventricular dynamics have been demonstrated in previous studies evaluating upright tilting,[22,23] the Valsalva maneuver,[24,25] ventricular premature beats[26] and normal phasic respiration.[14] Also, the response to acute pharmacologic interventions with agents such as amyl nitrite, nitroglycerin, isosorbide dinitrate, atropine and phenylephrine[11,22,27,28] have been successfully documented noninvasively in human beings with this technique. In addition, the beneficial effects of long-term therapy with oral prazosin in patients with congestive heart failure have been shown with echocardiography[29] as has the protective effect of long-term therapy with oral digoxin on left ventricular performance during acute pressure loading in normal persons.[9] Therefore, M mode echocardiography appears to be sufficiently sensitive in detecting meaningful changes in left ventricular dynamics due to various pharmacologic agents.

Role of acute pharmacologic pressure loading: Previous studies in animals[30] and man[31–33] have demonstrated that acute pharmacologic pressure loading results in a decrease in the rate of left ventricular shortening and can be used to assess left ventricular functional reserve in various disease states. Also, such pressure loading has been shown to be hemodynamically similar to isometric exercise.[33] Therefore, because patients can be successfully studied with echocardiography during this stressful intervention, we used it in an attempt to uncover latent left ventricular depression. Other types of stress would have been interesting to evaluate, but our patients with cardiomyopathy were too ill to undergo more vigorous interventions. It has previously been shown that patients with stable myocardial dysfunction can tolerate the degree of acute pressure loading we used.[34]

Clinical implications: Our results with M mode echocardiography demonstrate that small negative directional changes in left ventricular performance can be detected in normal subjects during long-term administration of oral quinidine at higher heart rates after atropine administration and that these changes are not seen in patients with compromised myocardial function. Furthermore, under the acute pressure load stress of intravenous phenylephrine, no significant differences in performance were observed in either the normal subjects or the patients with cardiomyopathy during treatment with quinidine as compared with placebo. These results are similar to those observed in a recent study with conscious previously instrumented dogs.[35] Therefore, any adverse effects on left ventricular performance produced by long-term administration of oral quinidine in therapeutic doses appears to be of little consequence.

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TABLE I

Data for 10 Normal Subjects

Stage	Drug	HR	SBP	Dd	%ΔD	Vd	Vpw
B	P1	68 ± 9	107 ± 9	42.6 ± 3.8	38.1 ± 5.8	1.22 ± 0.16	0.71 ± 0.06
	Q	74 ± 8†	109 ± 8	46.4 ± 4.4	36.6 ± 4.3	1.18 ± 0.15	0.68 ± 0.07
A	P1	99 ± 10	113 ± 7	44.6 ± 3.8	38.4 ± 5.8	1.44 ± 0.21	0.91 ± 0.13
	Q	93 ± 8	113 ± 8	46.3 ± 4.2	36.4 ± 4.0*	1.28 ± 0.19†	0.78 ± 0.12†
P	P1	94 ± 16	155 ± 9	46.9 ± 4.5	35.8 ± 7.1	1.21 ± 0.24	0.72 ± 0.15
	Q	91 ± 9	153 ± 9	47.2 ± 3.9	35.4 ± 5.4	1.17 ± 0.20	0.66 ± 0.08

* $P < 0.05$, paired t test comparing values during quinidine therapy with those during placebo administration.
† $P < 0.01$, paired t test comparing the values during quinidine therapy with those during placebo administration.
A = atropine; B = basal; Dd = left ventricular end diastolic dimension (mm), HR = heart rate (beats/min); P = phenylephrine; %ΔD = percent left ventricular dimension shortening; PI = placebo; Q = quinidine; SBP = systolic blood pressure (mm Hg); Vd = normalized rate of dimension shortening (sec^{-1}); Vpw = normalized posterior wall velocity (sec^{-1}).

rest or after atropine. During acute pressure loading heart rate was slower while the patients were taking quinidine, but the ejection phase indexes were not significantly lower.

Figure 1 illustrates the individual values for percent dimension shortening and normalized mean rate of dimension shortening for the eight patients before and after therapy with quinidine. In the basal state only one subject showed a modest decrease in left ventricular performance while taking quinidine as compared with the placebo control value. During acute pressure loading, two other subjects had a reduction in performance after quinidine. These two were among the three patients with the highest performance values during the study. The five patients with poorer compensation were not adversely affected by quinidine.

Discussion

Effects of quinidine on left ventricular function: Ferrer et al.,[15] using a single oral dose of 800 mg of quinidine, found that blood pressure was reduced in two thirds of their normal subjects and three fourths of their patients with various types of heart disease. However, no consistent changes in heart rate or cardiac output were observed. They hypothesized that this effect on blood pressure was largely due to a peripheral vasodilatory effect of quinidine, but that a small decrease in contractility could not be excluded. This blood pressure lowering effect was not observed by Visioli et al.[16] in their subjects who took 1.5 mg of quinidine orally in divided doses for 3 days. Also, we found no decrease in blood pressure in our subjects taking therapeutic doses of quinidine. Therefore, more prolonged oral therapy may be accompanied by compensatory mechanisms that offset any vasodilatory effect of quinidine.

In recent studies[16,17] systolic time intervals were used to assess noninvasively left ventricular performance in normal subjects taking oral quinidine. The modest changes in systolic time intervals demonstrated in these studies could be interpreted as a negative inotropic effect of quinidine. However, systolic time intervals depend on a constant relation between electric and mechanical events in the left ventricle, and quinidine is known to affect the time course of electric events.[1] Therefore, a change in the mechanical action of the heart cannot be inferred with certainty from systolic time intervals when the drug being studied is known to affect electric activity.

Our results in normal subjects suggest that quinidine may have a mild depressant effect on myocardial function that is masked by the vagolytic effect of the drug. In the basal state, heart rate was increased significantly during therapy with quinidine, but left ventricular ejection phase indexes were unchanged. After administration of atropine heart rate was similar with and without quinidine, but the performance indexes were decreased during administration of quinidine. However, these changes were small and the values attained were all in the normal range. Also, during acute

TABLE II

Data for Eight Patients With Cardiomyopathy

Stage	Drug	HR	SBP	Dd	%ΔD	Vd	Vpw
B	P1	75 ± 14	125 ± 17	66.5 ± 8.8	26.4 ± 12.5	1.01 ± 0.42	0.63 ± 0.20
	Q	81 ± 7	124 ± 17	65.9 ± 11.1	28.0 ± 13.0	1.13 ± 0.48	0.70 ± 0.25
A	P1	95 ± 13	123 ± 17	65.6 ± 10.5	26.1 ± 12.4	1.11 ± 0.44	0.72 ± 0.23
	Q	87 ± 14	123 ± 18	65.6 ± 11.3	26.3 ± 10.1	1.08 ± 0.41	0.71 ± 0.22
P	P1	85 ± 10	161 ± 20	67.0 ± 10.7	25.6 ± 11.3	0.99 ± 0.35	0.64 ± 0.16
	Q	79 ± 11*	159 ± 20	66.4 ± 10.4	25.6 ± 9.7	0.97 ± 0.25	0.60 ± 0.13

* $P < 0.05$.
Abbreviations as in Table I.

be potentially serious. Accordingly, we studied the effects of quinidine on left ventricular performance in normal subjects and patients with congestive cardiomyopathy with M mode echocardiography at rest and during acute pressure loading. Using this technique, we previously demonstrated[9] an improvement in left ventricular performance in normal subjects receiving oral digoxin.

Methods

Patients: The study group consisted of 10 normal subjects—5 men and 5 women aged 20 to 32 years—and 8 men with primary cardiomyopathy. The eight patients had previously undergone cardiac catheterization to establish the absence of coronary artery disease and to confirm symmetric left ventricular contraction. All the patients were well compensated with stable doses of oral digoxin and diuretic drugs. Serum digoxin levels were in the therapeutic range and the serum potassium was normal in all. No subject was taking any other medication and all were judged to be in clinically stable condition during the course of the study. Also, no patient had left bundle branch block, valvular heart disease or paradoxical septal motion on echocardiography. All subjects gave written consent to the study on forms approved by the University of Texas Health Science Center at San Antonio, Institutional Review Board.

Study protocol: The participants were given quinidine or a matched placebo in a randomized sequence, and the study protocol was performed after 3 to 7 days of drug administration. The normal subjects received 300 mg of quinidine four times daily, and serum levels at the time of the study 2 hours after the last dose averaged 3.6 ± 1.3 μg/ml. Only one subject had a value (0.8 μg/ml) below the therapeutic range of 2 to 5 μg/ml by this method[10] and one subject had a value higher than the therapeutic range (5.3 μg/ml). The eight patients received 200 to 400 mg of quinidine four times daily until a steady state therapeutic level was obtained. Their serum levels ranged from 2.9 to 4.8 μg/ml (mean 3.7 ± 0.7) 2 hours after the last dose.

The experimental protocol was begun by starting an intravenous infusion of 5 percent dextrose and water through a scalp vein needle. A baseline echocardiogram and measurements of heart rate and systemic arterial pressure (cuff sphygmomanometer) were obtained. Subsequently, atropine was administered intravenously in a quantity sufficient to raise the heart rate at least 30 beats/min or until a maximum of 1.5 mg had been given. When the heart rate and systemic arterial pressure were stable for at least 5 minutes, a second echocardiogram was obtained. At this point, with the reflex heart rate response to increased arterial pressure blocked by atropine, phenylephrine (10 mg diluted in 250 ml of 0.9 percent sodium chloride) was infused over 5 to 10 minutes in a quantity sufficient to raise the systolic arterial pressure approximately 40 mm Hg.[11] With systolic pressure held at this level, a third echocardiogram was obtained and the infusion terminated. The total volume of fluid used in the entire study did not exceed 50 ml.

Echocardiographic measurements: Echocardiograms were obtained on either a Picker Echoview 80-C coupled to an Irex Continutrace 101 recorder or an Electronics for Medicine Echo IV system. Echocardiograms of the left ventricle were taken from the standard intercostal space[12] along the left sternal border utilizing a hand-held transducer (2.25 or 1.9 megahertz) and were recorded on a strip chart recorder at a paper speed of 100 mm/sec. The R wave of the simultaneously recorded electrocardiogram was taken as the reference point, and end-diastolic dimension (Dd) of the left ventricle was measured at the level of the chordae tendineae. The end-systolic dimension (Ds) was measured as the smallest dimension between the left septal endocardium and the posterior wall endocardium during systole whether or not the two walls were exactly apposed.[13] Posterior wall excursion (PWE) was measured as the amplitude of wall motion from end-diastole. A simultaneous indirect carotid pulse tracing was also recorded to measure left ventricular ejection time (ET). Heart rate was calculated from the simultaneously recorded electrocardiogram.

All echocardiograms were performed with the subject in the same position, with the hand-held transducer in the same interspace and when the same anatomic landmarks were present in the echocardiogram. The echocardiographic measurements were made during expiration[14] and represent the average of at least five heartbeats.

From the echocardiographic measurements described, the percent left ventricular dimension shortening (%ΔD), the normalized mean rate of left ventricular dimension shortening (Vd) and the normalized posterior wall velocity (Vpw) were calculated as follows:

$$\%\Delta D = \frac{Dd - Ds}{Dd} \times 100$$

$$Vd = \frac{Dd - Ds}{Dd \times ET}$$

$$Vpw = \frac{PWE}{Dd \times ET}$$

The value of each measure with and without quinidine was compared for each stage of the study using the paired Student's *t* test with each subject serving as his or her own control.

Results

Normal subjects (Table I): In the basal state heart rate was significantly faster during quinidine administration than with placebo. However, systolic blood pressure, end-diastolic dimension, percent dimension shortening, normalized mean rate of shortening and normalized posterior wall velocity were not different. After intravenous administration of atropine, heart rate was increased as compared with the basal state, but was no different with and without quinidine. Blood pressure and end-diastolic dimension were also not different. The ejection phase indexes were all significantly less during quinidine therapy than during the post-atropine state with placebo. During infusion with phenylephrine, systolic blood pressure was higher than in either the basal or post-atropine state but there was no difference between any of the measurements studied with and without quinidine.

Patients with cardiomyopathy (Table II): The eight patients with cardiomyopathy underwent the same protocol as the normal subjects and the magnitude of change in heart rate after atropine and in blood pressure after phenylephrine was similar to that in the normal group. The group with cardiomyopathy differed from the normal subjects in having a larger end-diastolic dimension and lower ejection phase indexes. However, the group manifested no significant difference between the various measurements obtained with quinidine therapy and those obtained with placebo at

Effects of Oral Quinidine on Left Ventricular Performance in Normal Subjects and Patients With Congestive Cardiomyopathy

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To evaluate the effects of oral quinidine therapy on left ventricular performance, 10 normal subjects and 8 patients with cardiomyopathy were studied with echocardiography at rest, after intravenous injection of atropine and during infusion with phenylephrine. The echocardiographic studies were performed during oral quinidine therapy and during placebo administration. In the normal subjects heart rate was significantly faster with quinidine than with placebo (74 ± 8 (standard deviation) versus 68 ± 9 beats/min, $P < 0.01$), but there was no significant change in blood pressure or left ventricular size and performance. After administration of atropine, heart rate was identical with and without quinidine but the mean normalized velocity of left ventricular dimension shortening was significantly less with quinidine than with placebo (1.28 ± 0.19 versus 1.44 ± 0.21, $P < 0.01$). During acute pressure loading with phenylephrine there was no difference in left ventricular size or performance during quinidine therapy. In the patients with cardiomyopathy, no significant differences in left ventricular function were detected with this protocol during quinidine therapy. It is concluded that oral quinidine therapy appears to have little adverse effect on left ventricular performance at rest or during acute pressure loading.

Quinidine is one of the most commonly used antiarrhythmic drugs and has been considered by some to be the prototypic antiarrhythmic agent.[1] Early studies[2–4] in anesthetized dogs using intravenously administered quinidine in large doses (10 to 30 mg/kg body weight) demonstrated marked decreases in heart rate, blood pressure and contractile force measured by strain gauges sewn to the ventricular wall. Smaller doses (0.5 to 10 mg/kg) produced similar but less marked responses.[4–6] However, a recent study[7] in anesthetized open chest dogs after the intravenous administration of 4 to 8 mg/kg of quinidine demonstrated a decrease in heart rate, blood pressure and aortic blood flow but no significant change in rate of increase in left ventricular pressure (dP/dt). In a recent study[8] of patients with cardiac transplants given 10 mg/kg of quinidine intravenously, a significant decrease in blood pressure was accompanied by a decrease in cardiac output. Because there was no change in the left ventricular contractile state as determined with implanted metallic markers, it was concluded that venodilatation was the primary effect of the drug. Therefore, acute intravenous injection of quinidine in the experimental setting uniformly decreases heart rate and blood pressure, but changes in the contractile state of the left ventricle are more variable.

Because hypotension can be deleterious to critically ill patients, quinidine is currently most often used orally. However, little objective information is available concerning the effects of oral quinidine in the usual therapeutic doses on left ventricular performance in patients with cardiac disease in whom any depression of myocardial function would

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tachycardias always required an initiating beat. However, the absence of frequency-dependent acceleration of the tachycardia and its easy suppressibility by overdrive pacing are not consistent with triggered automaticity.

It is possible that isoproterenol facilitated reentry. One mechanism by which this might have occurred is the increase in the nonuniformity of recovery of excitability reported by Han et al.[29] A second mechanism may be related to the ability of isoproterenol to cause greater shortening of action potential duration in premature responses than in nonpremature responses without altering the rate of rise of the action potential.[25] By this mechanism, the refractory period should shorten, an effect that might permit reentry of a premature impulse. Another possibility by which isoproterenol might have facilitated reentry is by changing local metabolic conditions such as pH, extracell potassium and hypoxia either directly or by inducing ischemia. These changes might alter the electrophysiologic properties of the cell and facilitate the induction of reentry.

Pharmacologic studies in ventricular tachycardia: Wellens et al.[3] suggested that acute drug studies in patients with ventricular arrhythmias not only have therapeutic implications but may contribute to an understanding of the mechanisms responsible for the arrhythmias. The facilitation of induction of the ventricular tachycardia by isoproterenol in our study suggests that catecholamines may be important in the genesis of ventricular arrhythmias even when they are not exercise-induced. If this were true, we would have expected that propranolol would prevent the induction of these arrhythmias. However, propranolol was effective in counteracting the effects of isoproterenol in only four of nine patients. Three of these four patients also had exercise-induced ventricular tachycardia. The failure of propranolol to prevent the induction of tachycardia in the remaining five patients may indicate that the dose of administered propranolol was inadequate to block all of the effects of beta sympathetic stimulation even though it was adequate to prevent the increase in sinus rate in three of five nonresponders. This observation implies that the effects of beta sympathetic stimulation and blockade on the various cardiac tissues (sinus node, Purkinje and ventricular muscle fibers) and on the various electrophysiologic properties influenced by beta stimulation (the pacemaker currents and the slow inward and outward currents) may differ. It may also imply that the facilitating effect of catecholamines on induction of ventricular tachycardia may not be mediated by beta adrenergic receptor stimulation. It is also possible that patients with exercise-induced tachycardia are extremely sensitive to the arrhythmogenic influences of beta stimulation. This may explain the frequency with which arrhythmias developed spontaneously in such patients during the isoproterenol infusion and the fact that doses of propranolol smaller than those required to produce beta adrenergic blockade may be effective in suppressing these arrhythmias. The ability of procainamide to prevent the isoproterenol-induced facilitation of arrhythmia induction can be explained by the direct electrophysiologic effects of the drug, which would counteract the arrhythmogenic effects of isoproterenol.

Implications: In this study, isoproterenol did not cause any untoward effects. Its use as an adjunct to electric stimulation should aid in the performance of studies designed to determine appropriate therapy in patients with recurrent refractory ventricular tachycardia.

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on sinus rate disappeared. Ventricular tachycardia could be terminated in all nine patients by programmed single (Fig. 3) or double ventricular premature depolarizations or by rapid ventricular pacing (Table III).

Pharmacologic studies: After the administration of propranolol, isoproterenol failed to facilitate the induction of tachycardia in four patients (Cases 1, 3, 5 and 6) (Fig. 5). In the remaining five patients, ventricular tachycardia could still be initiated after propranolol and neither the zone nor the rate of tachycardia was changed. In three of these five patients (Cases 2, 10 and 11), the administration of procainamide prevented the initiation of ventricular tachycardia (Fig. 6). In two patients (Cases 4 and 8), propranolol and procainamide were ineffective in preventing initiation of tachycardia but the rate of tachycardia was reduced.

In two of five patients (Cases 4 and 10) (Table II) who did not respond to propranolol, the dose was inadequate to prevent the rate increase after rechallenge with the isoproterenol. In the remaining three patients (Cases 2, 8 and 11) and in all responders, the administered dose of propranolol was adequate to prevent the rate increase of rechallenge. The amount of isoproterenol used in the nonresponders was not significantly different from that used in the responders.

Exercise-related versus nonexercise-related ventricular tachycardia: Compared with nonexercise-related ventricular tachycardia, exercise-related ventricular tachycardia required a smaller dose of isoproterenol to initiate the tachycardia, was easier to induce and showed a greater degree of responsiveness to propranolol. Propranolol prevented the initiation of tachycardia in three of three patients with exercise-related tachycardia. In contrast, only one of six patients with nonexercise-related tachycardia responded to propranolol.

Discussion

Denes et al.[6] and Wellens et al.[8,9] demonstrated the failure of electric stimulation of the heart to induce ventricular tachycardia in patients with recurrent nonsustained ventricular tachycardia. Similar results have been reported in exercise-induced ventricular tachycardia.[8] Stimulation techniques have also been unsuccessful in initiating tachycardia in 10 to 50 percent of patients with recurrent sustained ventricular tachycardia.[5–7] In the present study, the administration of a small amount of isoproterenol permitted us to initiate the ventricular tachycardia by programmed stimulation in six of seven patients with recurrent nonsustained ventricular tachycardia and in three of four patients with recurrent sustained ventricular tachycardia. In each of these patients, stimulation techniques without isoproterenol failed to induce the tachycardia. Recent studies in patients with recurrent ventricular tachycardia have reported successful induction of ventricular tachycardia by left ventricular stimulation when right ventricular stimulation failed.[7] Because left ventricular stimulation was not performed in our study we cannot exclude the possibility that during control studies ventricular tachycardia could have been induced by left ventricular stimulation. Mason and Winkle[1] recently reported that isoproterenol administration facilitated the induction of ventricular tachycardia in two of five patients in whom it was tested, but they did not mention the dose used.

Isoproterenol and induction of ventricular tachycardia: Isoproterenol administration has been reported to reproduce those ventricular arrhythmias that can be induced by exercise.[16,17] In our study, tachycardia was exercise-related in three of the nine patients in whom the tachycardia was induced. In the fourth patient with exercise-induced tachycardia, isoproterenol did not spontaneously induce the tachycardia and did not facilitate the induction of tachycardia by the stimulation techniques employed.

The precise mechanism by which isoproterenol facilitated the induction of tachycardia in 9 of our 11 patients is uncertain. Beta adrenergic stimulation induces a variety of effects on the electrophysiologic properties of the single cell and on the intact heart (Table IV).[18–25] Which of these effects is responsible for the isoproterenol-induced facilitation of ventricular tachycardia induction in our patients is unclear. It is unlikely that enhanced automaticity can be incriminated as the responsible mechanism because arrhythmias induced by this mechanism are not usually triggered by premature stimuli or by pacing.[16,26,27] The tachycardias induced in our patients are similar in many ways to the fast idioventricular rhythms that occurred in dogs with induced complete atrioventricular block.[28] These arrhythmias always required an initiating beat, and overdrive pacing usually accelerated, rather than suppressed, the tachycardia. Vasalle et al.[28] suggested that triggered automaticity due to enhanced afterpotentials[23] might have been the underlying mechanism of the arrhythmias. In all but three of our patients, the

TABLE IV

Effects of Beta Adrenergic Agonists on Electrophysiologic Properties of Single Fibers and Intact Hearts

A. Single Fibers
1. Increase spontaneous phase IV depolarization of sinus node and Purkinje fibers[18,19]
2. Alter characteristics of I_{k1}, I_{k2}, I_{si}.*[20–22]
3. Facilitate development of triggered automaticity[23]
4. Shorten ventricular action potential duration in nonpremature action potentials[24]
5. Shorten action potential duration to a greater degree in premature than in nonpremature action potentials[25]
B. Intact Hearts
1. Increase sinus rate
2. Increase rate of ectopic pacemakers
3. Accelerate atrioventricular (AV) conduction
4. Shorten refractoriness of A-V node, His-Purkinje system and ventricular muscle

I_{k1} = non-time dependent outward potassium current; I_{k2} = pacemaker current.

* I_{si} = slow (calcium sensitive) inward current.

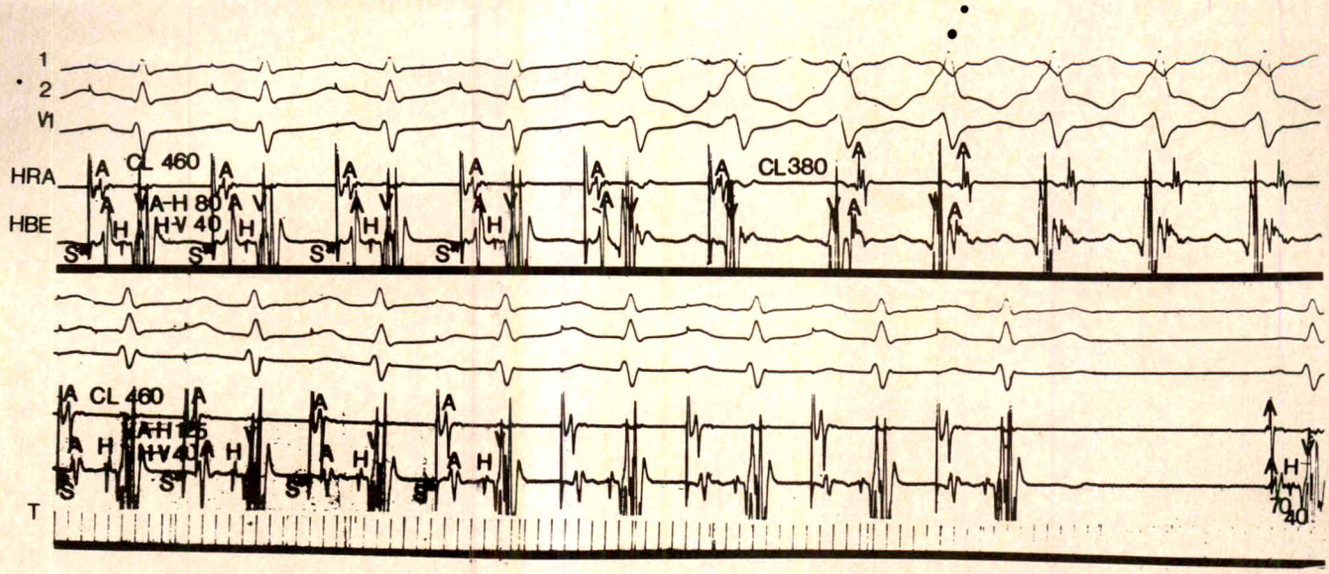

FIGURE 5. Case 5. Initiation of ventricular tachycardia by atrial pacing and the effect of propranolol on isoproterenol-induced ventricular tachycardia. After isoproterenol (6 μg) **(top panel)**, ventricular tachycardia could be initiated by atrial pacing at a cycle length (CL) of 460 msec. The A-H interval during atrial pacing measures 80 msec. The cycle length of ventricular tachycardia is 380 msec. After the administration of propranolol (0.05 mg/kg) **(bottom panel)**, rechallenge with isoproterenol and atrial pacing at the same rate as in the control study were no longer successful in initiating the tachycardia. Note the longer A-H interval after propranolol (80 versus 125 msec). Abbreviations as in Figure 1.

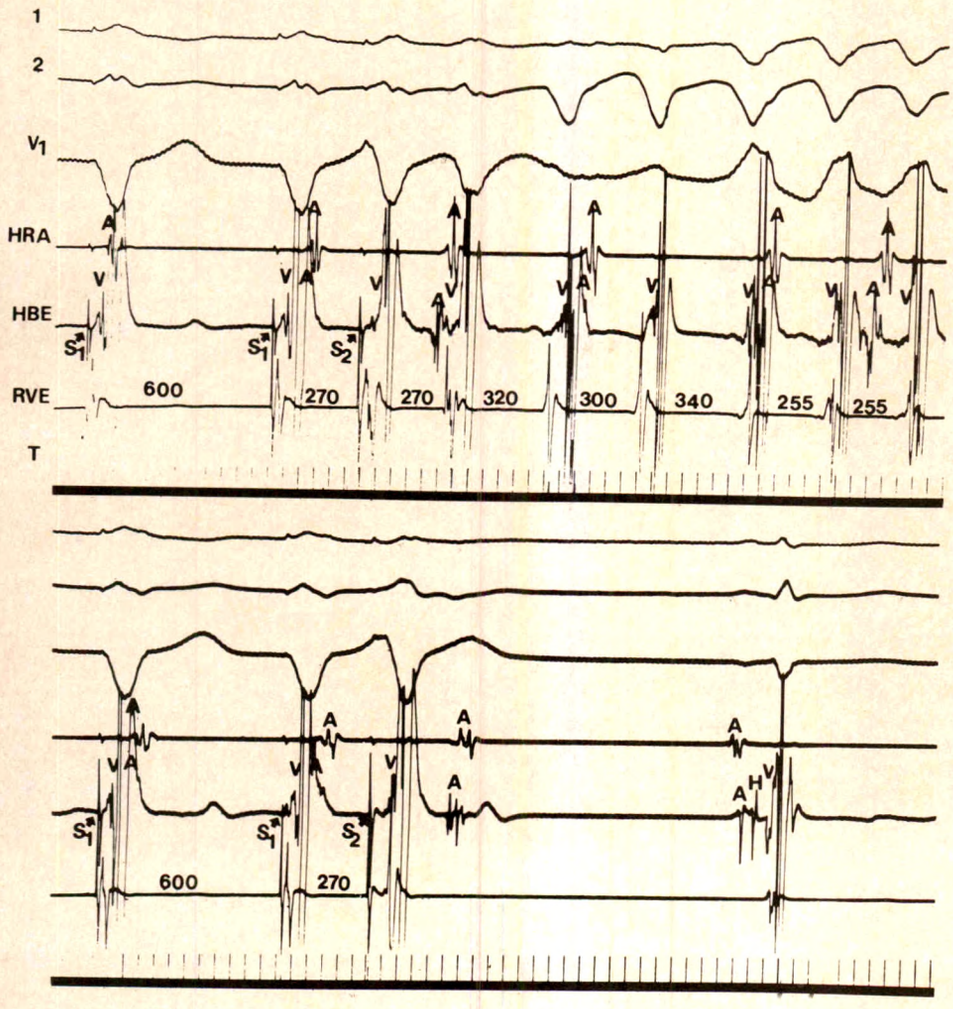

FIGURE 6. Case 1. (Same patient as in Figure 1). Isoproterenol-induced ventricular tachycardia and the effect of propranolol and procainamide. See Figure 1 for control study. In both panels, the right ventricle is paced at a cycle length (S_1-S_1) of 600 msec and the premature stimulus (S_2) is introduced at a coupling interval of 270 msec. Isoproterenol and stimulation techniques were still successful in inducing ventricular tachycardia after the administration of propranolol (0.1 mg/kg) **(top panel)** but not after the administration of procainamide (550 mg) **(bottom panel)**. The QRS pattern of tachycardia in lead I is different from that recorded during control studies (see Figure 1, **bottom panel**). After propranolol, the cycle length of tachycardia is 5 msec longer than the control cycle length.

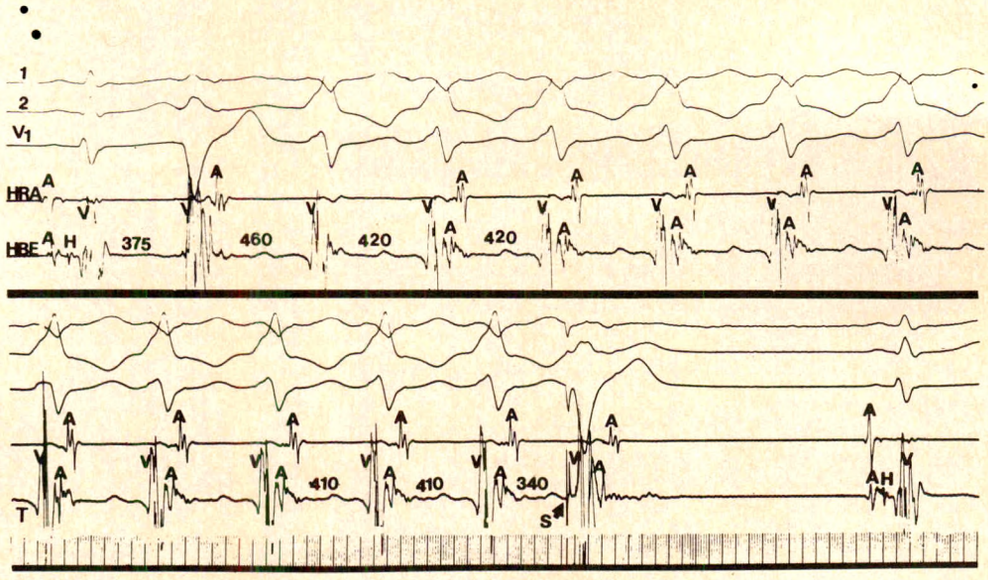

FIGURE 3. Case 5. Spontaneous initiation of tachycardia and termination by a single premature ventricular depolarization. After isoproterenol **(top panel)** ventricular tachycardia is abruptly initiated by a spontaneously occurring ventricular premature depolarization. Note that the QRS configuration of ventricular tachycardia is different from that of the initiating beat. Ventricular tachycardia is terminated by a single critically timed ventricular premature depolarization **(bottom panel)**. Time lines (T) are 10 and 50 msec apart. Abbreviations as in Figure 1.

tients (Cases 1, 5 and 6) rapid atrial pacing at rates of 130 to 150 beats/min initiated the tachycardia, which was also capable of being initiated by single ventricular premature depolarizations or rapid ventricular pacing (Fig. 5, Table III). In two of these patients (Cases 1 and 5) ventricular tachycardia also occurred spontaneously during the isoproterenol infusion. In an additional patient (Case 9), rapid atrial pacing could initiate and terminate the tachycardia but this effect could not be consistently reproduced.

In the two patients (Cases 1 and 5) in whom ventricular tachycardia occurred spontaneously after isoproterenol (Fig. 3), the arrhythmias were initiated by spontaneous ventricular premature depolarizations. The electrocardiographic configuration of these ventricular premature depolarizations was different from that of the subsequent tachycardia complexes (Fig. 3). In those patients in whom ventricular tachycardia could not be induced by the initial isoproterenol infusion, additional infusions of up to 30 μg were tested without success.

Termination of ventricular tachycardia: In all patients ventricular tachycardia was terminated by programmed stimuli before the effects of isoproterenol

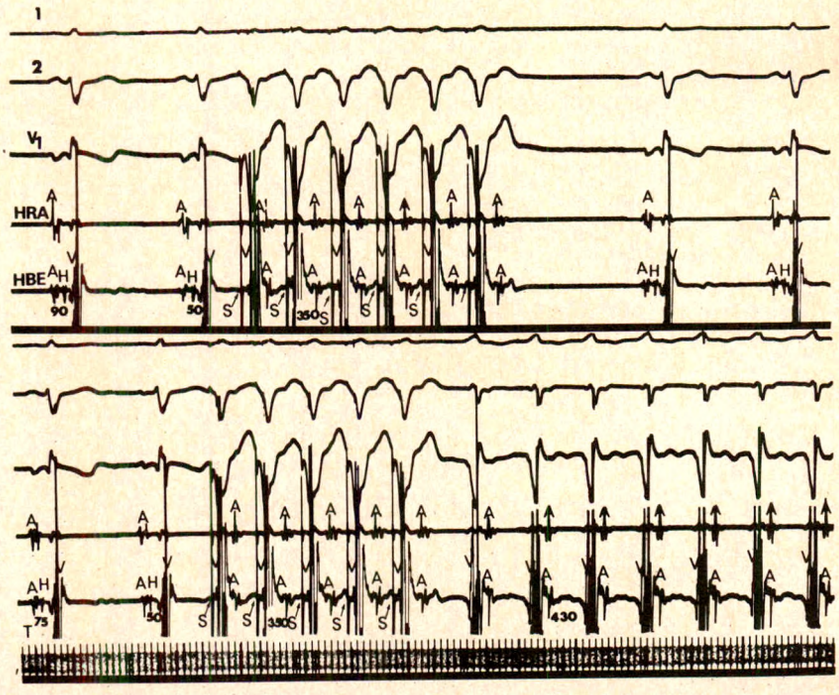

FIGURE 4. Case 10. Initiation of ventricular tachycardia by rapid ventricular pacing. During control studies **(top panel)**, ventricular pacing (S) at a cycle length of 350 msec failed to initiate ventricular tachycardia. After the administration of 12 μg of isoproterenol **(bottom panel)** ventricular pacing at the same cycle length as in the control study (initiated somewhat later in diastole) induces ventricular tachycardia, which has a cycle length of 430 msec. One to one retrograde conduction to the atria is present during ventricular tachycardia. Note the decrease in sinus cycle length from 1,000 to 850 msec and the decrease in A-H interval from 90 to 75 msec after isoproterenol. Time lines (T) are 10 and 50 msec apart. Abbreviations as in Figure 1.

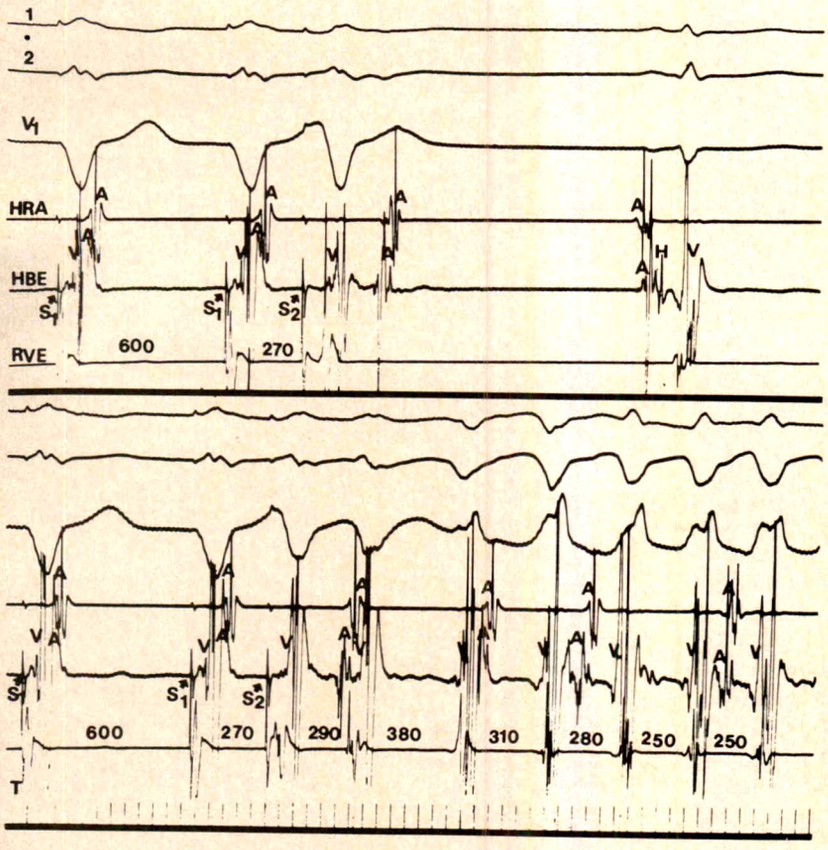

FIGURE 1. Case 2. Initiation of ventricular tachycardia after isoproterenol. The records are organized in both panels from **top to bottom** as follows: electrocardiographic leads I(1), II(2), V_1 and intracardiac electrograms from the high right atrium (HRA), His bundle (HBE) and right ventricle (RVE). The right ventricle is paced at a cycle length (S_1-S_1) of 600 msec. During control studies **(top panel)** a premature stimulus (S_2) introduced at a coupling interval of 270 msec fails to induce ventricular tachycardia and a sinus escape beat follows. Ventricular tachycardia could not be induced at shorter coupling intervals. After the administration of 10 μg of isoproterenol **(bottom panel)** a premature stimulus (S_2) introduced at a coupling interval identical to that of the control study initiates ventricular tachycardia that has a cycle length of 250 msec. Time lines (T) are 50 msec apart.

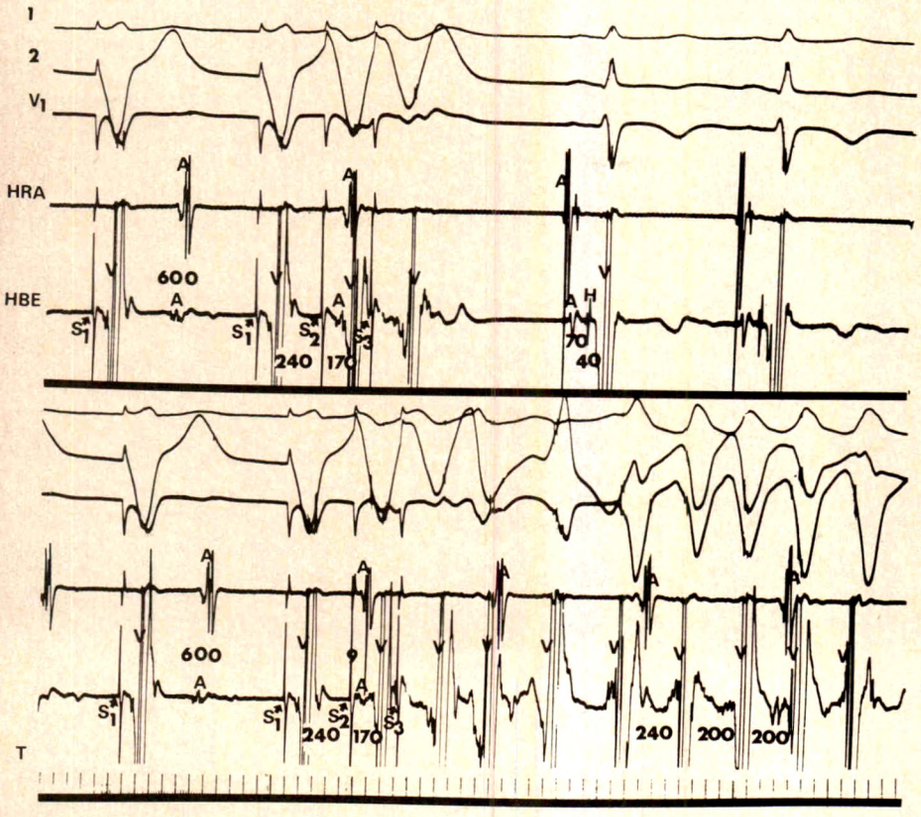

FIGURE 2. Case 11. Isoproterenol and ventricular tachycardia. The ventricular paced cycle length measures 600 msec. During control studies **(top panel)** double premature stimuli (S_2 and S_3) introduced at coupling intervals of 240 and 170 msec, respectively, failed to initiate ventricular tachycardia. After isoproterenol (10 μg) **(bottom panel)** two premature ventricular stimuli introduced at coupling intervals identical to those of the control study initiate ventricular tachycardia. Note the shortened retrograde conduction time (S-A) of basic drive beats after isoproterenol. Time lines (T) are 50 msec apart. Abbreviations as in Figure 1.

fractoriness failed to induce ventricular tachycardia, scanning with a second premature stimulus (S_3) was then performed. Two timed premature stimuli (S_2-S_3) were introduced starting at an S_1-S_2 interval that was 50 to 70 msec longer than the effective refractory period of the ventricle, and S_2-S_3 equal to the S_1-S_2 interval. The S_2-S_3 interval was then progressively shortened and when S_3 encountered ventricular muscle refractoriness, the S_1-S_2 interval was decreased until S_3 could elicit a ventricular response (V_3) or ventricular tachycardia. This protocol was continued until both S_2 and S_3 failed to evoke ventricular responses.

5. After the initiation of ventricular tachycardia timed single or double ventricular stimuli or short bursts of rapid ventricular pacing were used to terminate the arrhythmia. The extrastimuli used to terminate the arrhythmia were always applied at the same site of ventricular stimulation as that used to initiate the tachycardia.

Isoprotenol, propranolol and procainamide infusions: After the control studies using this protocol were performed, an isoproterenol solution containing 1 μg of isoproterenol/ml was infused intravenously at a rate of 1 to 2 μg/min to produce an increase in sinus rate of 15 to 25 beats/min.[14] Once the desired heart rate was reached, the stimulation protocol was repeated at comparable cycle lengths without altering the stimulus characteristics. In all patients, the effect of isoproterenol on sinus rate was present throughout the testing. Two to four such attempts to induce ventricular tachycardia were made in each of the 11 patients. The amount of isoproterenol required to induce the desired changes in heart rate ranged from 6 to 16 μg.

If the ventricular tachycardia could be induced after isoproterenol, the patients were then given propranolol (0.05 to 0.1 mg/kg) intravenously at a rate of 1 mg/min, and 15 to 20 minutes later isoproterenol was reinfused and stimulation studies were repeated. If ventricular tachycardia could still be induced, procainamide (10 mg/kg) was infused intravenously at a rate of 50 mg/min, the patients were rechallenged with isoproterenol and the stimulation studies were repeated. Heart rate and blood pressure were continuously monitored throughout the study.

Results

All patients tolerated the stimulation studies without any untoward effects. The effects of isoproterenol on heart rate and the A-H and H-V intervals were similar to those previously reported[15] (Table II). Isoproterenol shortened the sinus cycle length (806.36 ± 117 [mean ± standard deviation] versus 634 ± 104 msec, $P < 0.001$), shortened the A-H interval (91.9 ± 18 versus 78.6 ± 17 msec, $P < 0.001$) and had no effect on the H-V interval. The effective refractory period of the ventricle was shortened in all patients (239 ± 26 versus 218 ± 28 msec, $P < 0.001$).

Initiation of ventricular tachycardia: Before isoproterenol, ventricular tachycardia could not be initiated by any stimulation protocol method in any of the patients. After isoproterenol, ventricular tachycardia could be reproducibly initiated by one or two ventricular premature depolarizations or rapid ventricular pacing, or both, in 9 of 11 patients (Table III). The rates and morphologic features of the induced ventricular tachycardias were similar to those noted during spontaneous episodes.

Ventricular tachycardia was initiated by a single ventricular premature depolarization in eight patients (Fig. 1) and by two ventricular premature depolarizations in one patient (Fig. 2, Table III). In three patients (Cases 1, 5 and 6), the tachycardia could be initiated by ventricular premature depolarizations delivered during sinus rhythm (Fig. 3). In the remaining patients, tachycardia could be induced only by ventricular premature depolarizations delivered during ventricular pacing (Fig. 1). In each patient a reproducible tachycardia zone of 30 to 80 msec was present. An inverse relation of the coupling interval of the tachycardia-initiating ventricular premature beat (V_1-V_2 or V_2-V_3) to the interval from the ventricular premature beat to the first QRS complex of the tachycardia was observed in three patients (Cases 2, 10 and 11).

In four patients (Cases 1, 3, 5 and 10), ventricular tachycardia could be reproducibly initiated by ventricular pacing at rates of 120 to 160 beats/min (Fig. 4). There was no relation between the rate of the tachycardia and the rate of ventricular pacing. In three pa-

TABLE III

Initiation and Termination of Tachycardia

Case no.	Method of Initiation					Method of Termination				Induced VT		Spont VT	
	Spont	AP	VP	1VPD	2VPDs	AP	VP	1VDP	2VPDs	CL	QRS Pattern	CL	QRS Pattern
1	+	+	+	+	...	−	+	−	...	470	RBBB	430	RBBB
2	−	−	−	+	...	−	−	−	+	250	RBBB	280	RBBB
3	−	−	±	+	−	...	±	+	+	400	LBBB	420	LBBB
4	−	−	−	+	...	−	−	−	+	430	RBBB	450	RBBB
5	+	+	+	+	...	−	+	+	...	380	LBBB	400	LBBB
6	−	+	−	+	...	−	±	−	...	370	RBBB	400	RBBB
7	−	−	−	−	−	−	−	−	−	−	−	400	LBBB
8	−	−	−	+	...	−	−	+	...	410	RBBB	400	RBBB
9	−	±	−	−	−	+	−	−	−	270	RBBB	280	RBBB
10	−	−	+	+	−	−	+	−	+	430	LBBB	380 420	LBBB
11	−	−	−	−	+	−	+	−	+	240 220	LBBB	240	LBBB

+ = yes; − = no; ± = sometimes; . . . = not tested.
AP = atrial pacing; CL = cycle length; LBBB = left bundle branch block; RBBB = right bundle branch block; Spont = spontaneous initiation; VP = ventricular pacing; VPD = ventricular premature depolarization; VT = ventricular tachycardia.

TABLE I

Clinical Data

Case no.	Age (yr) & sex	Clinical Diagnosis	ECG
1	37M	Cardiomyopathy	Normal
2	52M	ASHD	Normal
3	54M	ASHD	Normal
4	58M	HCVD	LBBB
5	16F	No heart disease	SB
6	42F	Cardiomyopathy	LVH
7	58M	Cardiomyopathy	Normal
8	50M	ASHD	AWMI
9	52M	ASHD	Normal
10	70M	ASHD	AWMI
11	22M	No heart disease	Normal

ASHD = atherosclerotic cardiovascular disease; AWMI = anterior wall myocardial infarction; HCVD = hypertensive cardiovascular disease; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; SB = sinus bradycardia.

7), tachycardia was induced by exercise. In the remaining patients, the tachycardia occurred at rest but could not be provoked by exercise. The diagnosis of ventricular tachycardia was made using standard electrocardiographic criteria[10] and confirmed in all cases by intracardiac recordings during the arrhythmia. None of the patients had a myocardial infarction within the 6 months before the study. All patients had normal serum potassium, and cardioactive drugs were discontinued in all at least 48 hours before the study.

Electrophysiologic studies: These were performed with the patient in the postabsorptive nonsedated state after informed consent was obtained. Normal sinus rhythm was present in all patients at the time of study. Bundle of His electrograms were recorded as previously described using a no. 7 tri- or quadripolar electrode catheter.[11] A no. 6 quadripolar electrode catheter was introduced into an antecubital vein and advanced to the high right atrium for pacing and recording the local electrogram. An additional no. 6 bi- or quadripolar electrode catheter was percutaneously introduced into a separate antecubital vein and positioned at the right ventricular apex for ventricular stimulation and recording of a local electrogram. Atrial and ventricular stimulation was performed using a programmable digital stimulator (Designed by Bloom Associates, Philadelphia) that delivered rectangular pulses of 1.5 msec in duration at twice diastolic threshold. Intracardiac electrograms and electrocardiographic leads I, II and V_1 were simultaneously displayed on a multichannel oscilloscope (VR-12 Recording System, Electronics for Medicine) and recorded on paper moving at a speed of 50 to 100 mm/sec.

Anterograde and retrograde refractory period studies were performed at one or more basic cycle lengths (S_1-S_1), ranging from 950 to 550 msec, using the extrastimulus method.[12] After every eighth beat of the basic drive, a premature beat (S_2) was introduced at progressively decreasing (10 to 20 msec) coupling (S_1-S_2) intervals up to the onset of atrial or ventricular refractoriness.

Definition of terms:

S_1-S_1 = basic paced cycle length.

S_1-S_2 = coupling interval from eighth beat of a basic cycle length to the first premature beat.

S_3 = second premature beat delivered after S_2 during a basic cycle length, S_1-S_1.

S_2-S_3 = coupling interval between the first and second premature stimuli.

$V_1V_2V_3$ = ventricular depolarizations produced by S_1, S_2 and S_3, respectively.

Tachycardia zone = range of S_1-S_2 or S_2-S_3 coupling intervals during which ventricular tachycardia could be initiated.

Effective refractory period of ventricle[13] = the longest S_1-S_2 interval at which S_2 does not evoke a ventricular response.

The following protocol of programmed stimulation was utilized:

1. Incremental atrial pacing (maximal rates of 130 to 200 beats/min).
2. Premature atrial stimuli during sinus rhythm or atrial pacing, or both.
3. Incremental ventricular pacing with abrupt cessation after each increment of 10 beats/min (maximal pacing rates 140 to 220 beats/min) was performed for periods ranging from 10 to 60 seconds.
4. Ventricular extrastimulus testing during sinus rhythm and ventricular pacing at one or more cycle lengths. Ventricular pacing was performed from the right ventricular apex in all patients. In six patients (Cases 2, 3 and 8 to 11) ventricular stimulation was performed from both the right ventricular apex and outflow tract. If scanning with a single ventricular premature stimulus (S_2) from late diastole to ventricular re-

TABLE II

Electrophysiologic Data

Case no.	Sinus CL		A-H interval		H-V interval		ERP-V		Dose of Propranolol (mg/kg)
	C	Iso	C	Iso	C	Iso	C	Iso	
1	750	550	90	80	55	55	220	<240	0.1
2	750	600	75	65	55	55	220	190	0.1
3	800	600	120	110	60	60	240	220	0.1
4	900	700	100	80	80	80	280	260	0.05
5	1000	820	65	60	40	40	280	260	0.05
6	820	600	100	90	55	55	230	200	0.1
7	800	600	120	105	60	60	260	230	
8	700	550	90	75	60	60	230	210	0.1
9	700	550	80	65	50	50	230	210	0.1
10	1000	830	90	75	50	50	220	200	0.1
11	650	550	70	60	40	40	200	190	0.05

A-H interval = atrioventricular nodal conduction time; C = control period; CL = cycle length; ERP-V = effective refractory period of ventricle; H-V interval = His-Purkinje conduction time; Iso = isoproterenol.

Use of Isoproterenol As an Aid to Electric Induction of Chronic Recurrent Ventricular Tachycardia

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Initiation of ventricular tachycardia using isoproterenol administration and programmed stimulation of the heart was attempted in 11 patients with recurrent ventricular tachycardia in whom standard stimulation techniques alone failed to induce the tachycardia. Seven patients had nonsustained and four had sustained ventricular tachycardia. In four patients, ventricular tachycardia was induced by exercise; in the remaining seven, tachycardia was not exercise-induced. Before isoproterenol, single and double ventricular premature depolarizations and rapid ventricular pacing failed to induce the tachycardia in all patients. After intravenous administration of small amounts (6 to 16 μg) of isoproterenol, critically timed single and double ventricular premature depolarizations could reproducibly initiate and terminate the tachycardia in six of seven patients with nonsustained ventricular tachycardia and in three of four patients with sustained ventricular tachycardia. Propranolol (0.05 to 0.1 mg/kg body weight) was effective in blocking the arrhythmia-facilitating effect of isoproterenol in four patients and procainamide (10 mg/kg) was effective in three patients. In two patients, neither propranolol nor procainamide was effective.

The precise mechanisms underlying the arrhythmogenic effects of isoproterenol in each patient are not obvious. Nonetheless, our results suggest that the administration of isoproterenol is a useful adjunct when attempting to initiate ventricular tachycardia by stimulation techniques. As such, it should be helpful in carrying out studies designed to establish appropriate therapeutic interventions in patients with recurrent ventricular tachycardia.

Chronic recurrent ventricular tachycardia is frequently refractory to treatment with standard doses of antiarrhythmic drugs. Acute drug testing as a rapid screening method has been advocated to solve this problem.[1–4] To conduct such studies, however, the tachycardia must be repeatedly induced by electrical stimulation. In 10 to 50 percent of patients with chronic recurrent ventricular tachycardia, the tachycardia cannot be induced by electrical stimulation.[5–9] In this paper, we report results obtained when small doses of isoproterenol were administered to 11 consecutive patients with symptomatic recurrent ventricular tachycardia in whom standard stimulation techniques failed to induce tachycardia.

Methods

Patients: The pertinent clinical data for each of the 11 patients are presented in Table I. Seven patients (Cases 1 to 7) had nonsustained and four (Cases 8 to 11) had sustained ventricular tachycardia. Nonsustained tachycardia usually lasted only for seconds to minutes and was self-terminating. Sustained tachycardia lasted for minutes to hours and always required termination by drugs or direct current cardioversion. All patients exercised on the treadmill using a standard Bruce protocol prior to stimulation studies. In four (Cases 1, 5, 6 and

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beats/min attained by our subjects should reflect the achievement of a level of exercise at or near maximal oxgyen consumption.

In our study, the mean heart rates did not return to preexercise levels within 10 minutes after exercise was stopped. Preliminary data in our laboratory[19] show that serum catecholamines are still elevated at 10 minutes after exercise, perhaps explaining this phenomenon. Our protocol's requirement that subjects stand rather than sit or lie after exercise may also have contributed to the persistent postexercise elevation in heart rate.

Blood pressure responses: Obtaining blood pressures during exercise has achieved increasing importance both in adults with coronary artery disease[20] and in children with congenital heart defects.[21] Current guidelines for exercise testing indicate the importance of obtaining blood pressures during the test.[22] Blood pressures obtained from children exercising on the bicycle have previously been reported,[21,23] but pressures obtained during treadmill exercise in children have not been published. Our data reveal that the greatest rise in systolic pressure occurs in the 1st minute of exercise (Fig. 2). Thereafter, there is a more gradual increase in pressure until peak exercise is achieved. There is a progressively higher rise in systolic pressures with size and age, as illustrated by the progressively greater rises and peak pressures from group I through group IV (Fig. 2, Table III). Diastolic pressures tend either to remain constant or to decrease during exercise, resulting in a larger pulse pressure at peak exercise from the smallest to the largest children ($P < 0.001$).

Some reports[13,24,25] have shown that among older adolescents, basal blood pressures in boys are greater than those in girls. Preexercise systolic and diastolic pressures in our study revealed no consistent differences between boys and girls. At peak exercise, however, older boys had significantly greater systolic pressures than girls of the same subgroup. The absolute peak systolic blood pressures of group IV were very similar to those recently reported for healthy men in a study using a similar protocol.[26]

Several studies[27–29] have shown that systolic and diastolic blood pressures at rest become significantly higher in blacks than in whites with advancing age. However, Londe et al.[24] and others[25,30] have shown that during the first 2 decades of life there is little difference between the blood pressures of black and white children. Our preexercise values for systolic blood pressure during standing (Table III) show that black children tended to have higher systolic pressure levels than white children, but the differences were not significant. However, preexercise diastolic pressures were higher in older black children (Group III, Table IV), although these differences disappeared at maximal exercise.

The excellent reproducibility of systolic blood pressure responses with repeated exercise tests demonstrated in our study suggests that blood pressure determinations might be a valuable tool in the evaluation of such defects as coarctation of the aorta and aortic stenosis.

Changes in rate-pressure product: This product has been reported as an index of myocardial oxygen consumption during exercise.[31,32] Changes in the product of heart rate and blood pressure parallel changes in myocardial blood flow and myocardial oxygen consumption in normal men during upright exercise.[31] This product provides an index for comparative studies and might be applicable in evaluating children with suspected compromise of the myocardium due to congenital or acquired heart disease or dysfunction.

S-T and T wave changes: The increase in T wave amplitude during exercise seems to be a consistent feature. Lack of this increase, a decrease or an inversion of the T wave has been seen in our laboratory in patients with myocardial impairment. Changes in S-T segment during exercise in adults have been well described,[33–35] and the same guidelines apply to children. In our series, all children had upward sloping S-T segments almost immediately after the J point and certainly by 0.08 second after the J point. Considerable depression of the J point is often seen with fast heart rates. However, in our patients the J point was always on a line extended from the previous P to Q points. This line may offer a better estimation of the baseline from which to evaluate J point and S-T segment deviations.[23,26]

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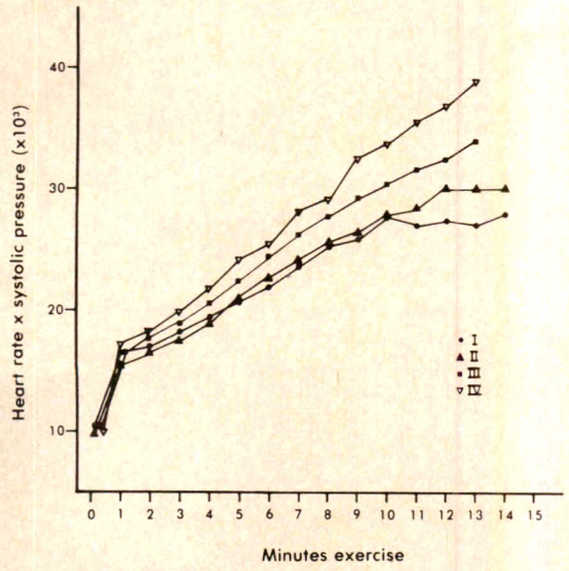

FIGURE 3. Means of heart rate × systolic pressure (double product) at each minute of exercise for the four groups.

TABLE V

Estimated Energy Expenditure[16]

Treadmill Elevation (%)	Estimated O_2 Uptake (ml O_2/kg per min)	Energy Expenditure (METS*)
0	12.34	3.52
2	15.72	4.49
4	19.09	5.45
6	22.48	6.42
8	25.85	7.39
10	29.23	8.35
12	32.61	9.32
14	36.00	10.29
16	39.37	11.25
18	42.75	12.21
20	46.13	13.18
22	49.51	14.15
24	52.89	15.11
26	56.27	16.08
28	59.65	17.05

1 MET = energy expenditure at rest = 3.5 ml O_2/kg body weight per minute.

chest pain (4 subjects), trivial pulmonary stenosis with a gradient of less than 20 mm Hg (5 subjects) and mild aortic stenosis with a gradient of less than 30 mm Hg (11 subjects). Most children had repeated tests 1 year apart, although two subjects had their tests repeated 2 years apart.

Correlation between the first and second test was $r = 0.85$ ($P < 0.001$) for heart rate before exercise and $r = 0.74$ ($P < 0.001$) for the rise in heart rate from before exercise to peak exercise. The correlation coefficient was $r = 0.94$ ($P < 0.001$) for systolic blood pressure before exercise and $r = 0.80$ ($P < 0.001$) for peak systolic pressure. Correlations of $r = 0.46$ and $r = 0.26$ were found between diastolic pressure before exercise and peak diastolic pressure, respectively; neither value was significant.

Discussion

Advantage of the treadmill exercise protocol: The treadmill protocol used in this study seems most suited for the testing of children. They adapt very easily early in the test periods, settling into a brisk walk. The fixed speed of the protocol keeps the children from having to change pace and decreases the risk of falling. It also simplifies physiologic measurements, because walking causes less bouncing than running. The heart rate and blood pressure increase promptly, then remain constant during each minute of a particular grade elevation. Few children, even athletes, complete the entire procotol of 15 minutes of exercise, revealing the ability of the protocol to stress the cardiovascular system. It must be emphasized that the slightest support during exercise may reduce the metabolic cost of work and prolong exercise time to the point of boredom and lack of motivation of both the subject and the laboratory staff.

No comparison was made between the modified Balke protocol and other protocols in our laboratory. However, the exercise of children on the treadmill using the Bruce protocol was recently well described by Cumming et al.,[12] although they did not report blood pressure responses. These authors preferred the Bruce protocol to a constant speed protocol, because they believed that the latter protocol caused exercise to last too long, with boredom becoming a factor and the grade becoming too steep before exhaustion. However, their constant speed protocol used very slow treadmill speeds (2.0 and 2.5 miles/hour), resulting in maximal exercise effort only after very long periods of time. The speed of 3.5 miles/hour used in our study allowed the test to be much shorter, and fatigue was reached within 10 to 12 minutes. The ability to obtain blood pressures during treadmill exercise is probably the greatest advantage of this protocol, because jerky movements are held to a minimum.

Exercise endurance time: The mean duration of exercise (endurance time) for all children tested was 10.0 ± 1.3 minutes. Endurance times using the Bruce protocol[12] for children in similar age groups averaged between 12 and 13 minutes. In our series, boys exercised for longer periods of time as their body size increased (Table I), but girls' endurance times did not increase in the same manner. These findings are similar to those obtained with the Bruce protocol.[12]

Heart rate responses: Two phases of heart rate responses were observed. First, there was a rapid increase in heart rate during the 1st minute of exercise, and then a linear increase in heart rate occurred until peak exercise was reached. Peak exercise heart rates were similar in all groups regardless of sex or race. Cumming et al.,[12] using the Bruce exercise protocol, also found no differences in maximal heart rate between boys and girls. Their maximal heart rates were slightly greater than those achieved by our subjects. It has been shown[17,18] that maximal oxygen consumption is approached when the heart rate is 180 beats/min or greater; therefore, the mean heart rate of 187 ± 14

TABLE III

Systolic Blood Pressure (mm Hg ± 1 standard deviation)

	Group I		Group II		Group III		Group IV	
	W	B	W	B	W	B	W	B
Boys								
no.	(28)	(15)	(41)	(19)	(44)	(19)	(6)	(6)
Pre Ex	107 ± 9	121 ± 12	108 ± 12	113 ± 8	118 ± 13	124 ± 11	128 ± 5	119 ± 10
1 Min Ex	121 ± 12	129 ± 16	121 ± 14 †	131 ± 9	137 ± 17	139 ± 11	150 ± 10	146 ± 14
Peak Ex	142 ± 16	145 ± 16	145 ± 15	154 ± 17	171 ± 22	181 ± 16	206 ± 9	200 ± 22
Girls					‡	*		§
no.	(19)	(10)	(21)	(11)	(25)	(22)	(1)	(1)
Pre Ex	110 ± 9	113 ± 13	106 ± 12	112 ± 11	112 ± 10 ‡	118 ± 7 §	124	100
1 Min Ex	123 ± 11	123 ± 13	122 ± 14	128 ± 15	126 ± 14	141 ± 17	150	122
Peak Ex	147 ± 12	145 ± 14	145 ± 13	154 ± 24	155 ± 14	161 ± 20	184	140

* $P < 0.05$.
† $P < 0.02$.
‡ $P < 0.01$.
§ $P < 0.005$.
B = black; no. = number of subjects; 1 Min Ex = 1 minute of exercise; Peak Ex = peak exercise; Pre Ex = before exercise; W = white.

(Fig. 3). The double product responses were similar for all groups during early exercise, becoming more divergent later in the exercise period.

Electrocardiogram: *Rhythm:* All children maintained sinus rhythm throughout the test.

T wave: The mean T wave amplitude for all groups increased from 4.8 ± 2.5 mm at rest to 7.3 ± 2.8 mm at maximal exercise effort and returned to normal during the postexercise period.

S-T segment: At fast heart rates, such as those achieved during exercise, a J point depression often occurred. However, in all our studies, the S-T segment had an immediate upward slope. No child had a flat or downward S-T segment at 0.08 second after the QRS complex.

Estimated energy expenditure: The estimated energy expenditure achieved at the completion of each stage of the protocol is listed in Table V. These were calculated using the formula of Balke and Ware[15] for treadmill exercise.

Comparison of amplified Korotkoff sounds with standard stethoscope: Blood pressures were obtained in rapid succession using the NARCO Amplification device and a standard stethoscope but with the same cuff in 21 children. The correlation coefficient (r) for systolic blood pressures was 0.96 and for diastolic pressures 0.90.

Reproducibility: Twenty children not from our reference population underwent repeated exercise tests because of minor complaints such as musculoskeletal

TABLE IV

Diastolic Blood Pressure (mm Hg ± 1 standard deviation)

	Group I		Group II		Group III		Group IV	
	W	B	W	B	W	B	W	B
Boys								
no.	(28)	(15)	(41)	(19)	(44)	(19)	(6)	(6)
Pre Ex	74 ± 7	79 ± 9	75 ± 11	79 ± 11	79 ± 9	85 ± 10	85 ± 9	80 ± 9
1 Min Ex	76 ± 6	82 ± 9	77 ± 9	81 ± 8	83 ± 12	80 ± 4	86 ± 9	85 ± 10
Peak Ex	85 ± 7	85 ± 7	84 ± 9	87 ± 9	77 ± 12	84 ± 11	95 ± 8	87 ± 11
Girls								‡
no.	(19)	(10)	(21)	(11)	(25)	§ (22)	(1)	(1)
Pre Ex	71 ± 9	77 ± 5	76 ± 7	74 ± 8	78 ± 6	84 ± 7	92	96
1 Min Ex	74 ± 9	82 ± 4	79 ± 7	83 ± 12	81 ± 9	† 89 ± 11	96	92
Peak Ex	79 ± 7	83 ± 4	84 ± 6	85 ± 11	79 ± 10	84 ± 12	110	100

* $P < 0.05$.
† $P < 0.02$.
‡ $P < 0.01$.
§ $P < 0.005$.
B = black; no. = number of subjects; 1 Min Ex = 1 minute of exercise; Peak Ex = peak exercise; Pre Ex = before exercise; W = white.

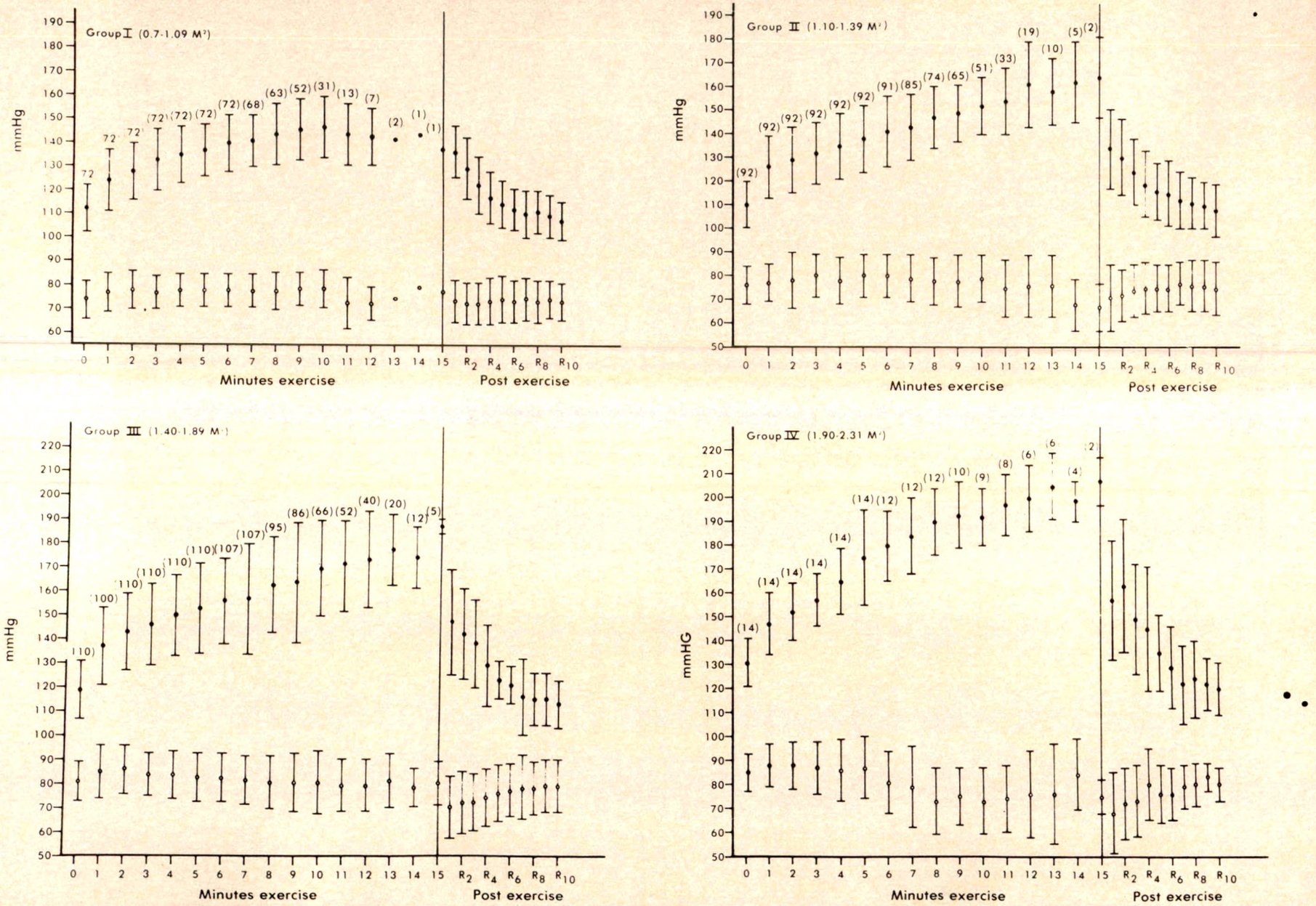

FIGURE 2. Mean (± 1 standard deviation) systolic (**closed circles**) and diastolic (**open circles**) blood pressures at each minute during and after exercise in the four groups. Numbers in parentheses indicate the number of subjects exercising at that minute. R2, R4, indicate values obtained during the 10 minute postexercise period.

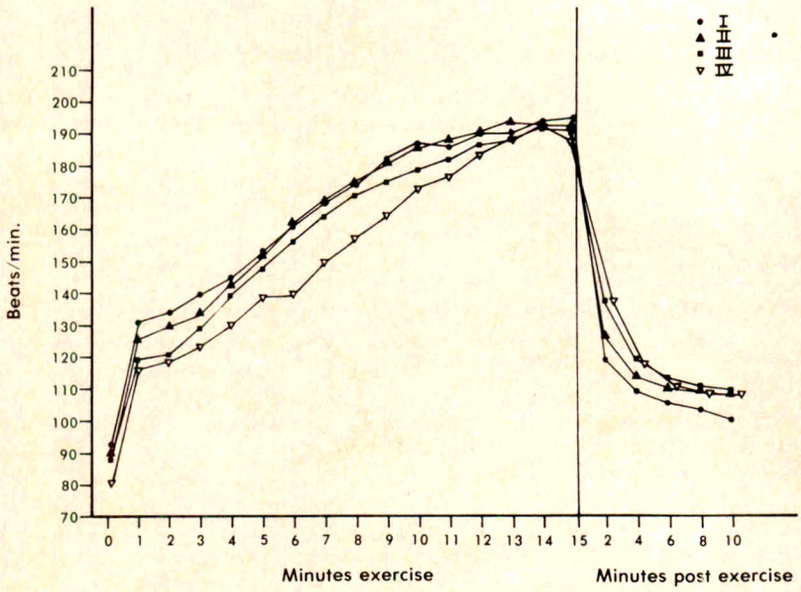

FIGURE 1. Mean heart rates at each minute of exercise and in the postexercise period for the four groups classified according to body surface area.

Blood pressure responses: The mean minute to minute systolic and diastolic responses of the children are illustrated in Figure 2. The systolic pressure elevation was greatest in the 1st minute of exercise in all age groups. A more gradual increase in systolic pressure occurred thereafter. The rate of increase in systolic pressure and the absolute level attained were greater in each succeeding group with a larger body surface area. Diastolic pressures remained relatively constant during exercise and even tended to decrease in the older children, resulting in an increased pulse pressure during exercise, with the peak pulse pressure being greater in each succeeding group ($P < 0.01$ between each group).

Table III lists the values of systolic blood pressure before exercise, at 1 minute of exercise and at peak exercise for all the groups further classified according to sex and race. No differences were found between boys and girls in the values before exercise. Black girls in group III had significantly greater systolic pressures before exercise than white girls of the same group. At 1 minute of exercise, some subgroups of black children had significantly greater pressures than white children in groups II and III. Differences between girls and boys after 1 minute of exercise were seen only in the white children in group III. At peak exercise, male-female differences were demonstrated by both races only in group III.

Table IV lists the diastolic pressures in similarly classified subgroups. Diastolic pressures in the black children of group II were significantly greater before exercise, but at peak exercise these differences were not significant.

Heart rate-blood pressure product: The heart rate-blood pressure product (double product) was calculated by multiplying the heart rate by systolic pressure at each minute of exercise for each child. The mean of the double product at each minute of exercise was calculated for each of the four body surface area groups

TABLE II

Heart Rates (beats/min ± 1 standard deviation)

	Group I		Group II		Group III		Group IV	
	W	B	W	B	W	B	W	B
Boys								
no.	(28)	(15)	(41)	(19)	(44)	(19)	(6)	(6)
Pre Ex	91 ± 13	91 ± 15	91 ± 10	88 ± 19	87 ± 13	80 ± 12	85 ± 14	76 ± 11
1 Min Ex	131 ± 14	130 ± 12	123 ± 10	122 ± 18	116 ± 14	115 ± 14	117 ± 16	113 ± 16
Peak Ex	183 ± 13	179 ± 14	186 ± 15	185 ± 17	192 ± 12	186 ± 7	190 ± 15	181 ± 21
Girls								
no.	(19)	(10)	(21)	(11)	(25)	(22)	(1)	(1)
Pre Ex	94 ± 16	93 ± 12	96 ± 13	83 ± 8	93 ± 13	88 ± 12	90	100
1 Min Ex	129 ± 12	135 ± 14	129 ± 15	125 ± 7	131 ± 14	129 ± 12	137	151
Peak Ex	187 ± 10	194 ± 8	191 ± 9	185 ± 13	191 ± 16	186 ± 8	191	181

* $P < 0.02$.
† $P < 0.005$.
‡ $P < 0.001$.
B = black; no. = number of subjects; 1 Min Ex = 1 minute of exercise; Peak Ex = peak exercise; Pre Ex = before exercise; W = white.

TABLE I

Duration of Exercise (min ± 1 standard deviation)

	Group I*		Group II*		Group III*		Group IV*	
	W	B	W	B	W	B	W	B
Boys	10 ± 2 (28)	10 ± 2 (15)	11 ± 2 (41)	11 ± 1 (19)	12 ± 2 (44)	11 ± 3 (19)	13 ± 2 (6)	10 ± 3 (6)
Girls	9 ± 1 (19)	9 ± 1 (10)	9 ± 2 (21)	8 ± 1 (11)	9 ± 2 (25)	9 ± 2 (22)	9 (1)	5 (1)

* Group I = body surface area (BSA) 0.72 to 1.09 m^2; Group II = BSA 0.10 to 1.39 m^2; Group III = BSA 1.40 to 1.89 m^2; Group IV = BSA 1.90 to 2.31 m^2.
B = black; W = white.
Figures in parentheses indicate number of subjects.

to 1.89 m^2), 110 subjects; and group IV (1.90 to 2.31 m^2), 14 subjects. This subject grouping was chosen because hemodynamic responses change with size and age. Group IV contained fewer subjects than the other groups because subjects with a body surface area greater than 1.9 m^2 are usually beyond the pediatric age range. This group and its subsets were thought to be too small to include in statistical analysis, but their data are presented because the results form a transition to adult exercise data.

Equipment: All children exercised on a treadmill (Collins model P-2000 E). Blood pressures were obtained from the left arm while the child was standing before, during and after the exercise period; standard blood pressure cuffs were used with a small microphone over the brachial artery beneath the cuff (NARCO Bio Systems Programmed Electro-Sphygmometer PE-300). This apparatus amplified all phases of the Korotkoff sounds, so that blood pressure recordings could be obtained by auscultation from a standard mercury manometer during exercise. Three cuff sizes were used (9.5, 12.5 and 15.5 cm wide); cuffs were selected so that the bladder covered at least two thirds of the upper arm length and completely encircled the arm.[13,14] The blood pressure cuff was inflated every minute during exercise and also each minute of the 10 minute postexercise period. The fourth Korotkoff sound was used for diastolic pressures.*

The heart rate, electrocardiogram and S-T segment deviations were constantly monitored (Avionics Stress Test Monitor, model 2900-B), and a 10 second electrocardiographic strip was recorded at the end of each minute of exercise. For this purpose, the skin was cleansed with acetone, and adhesive electrodes were securely fastened to the skin with tape. Lead CM_5 was used as the monitoring electrode.

Treadmill protocol: The protocol used was similar to that described by Balke and Ware[15] but as altered by Austin et al.[16] It consisted of a constant treadmill speed of 3.5 miles/hour with a 2 percent elevation of the grade at the end of each minute of exercise. At this speed, the gait is a fast walk and the measurement of physiologic data is facilitated. Children aged 4 to 6 years sometimes exercised at a speed of 3.0 or 2.5 miles/hour to prevent running and to maintain the same gait as that of older children. This can be timed with a metronome at a setting of 124. To avoid dissipation of work forces, children were instructed not to hold on to the rail or to use other means of support during the test. The protocol allows a very even mode of exercise with a gradual increase in work. Exercise was continued for the maximal time allowed (15 minutes) or until severe fatigue prevented further exercise. The latter end point was manifested by refusal by the child to exercise further, jumping off the treadmill or falling back into the person standing behind him or her. Data for children not believed to achieve peak exercise effort were not included in this study. After peak effort was reached, a walk-down period of 2 to 3 minutes was allowed at level grade with a very slow treadmill speed to prevent exaggerated vagal responses. The remaining heart rate and blood pressure determinations during the 10 minute postexercise period were obtained during standing so that comparisons could be made with data obtained during exercise.

Data analysis: Confidence limits were established with use of Student's *t* test. A probability (*P*) value of <0.05 was considered significant. Grouped data are given as means ±1 standard deviation.

Results

Duration of exercise: Table I shows the mean duration of exercise for each of the four groups based on body surface area. There was an increase in exercise duration from the smaller to the larger boys that was not evident in girls. The average duration of exercise for all groups was 10.0 ± 1.3 minutes. Girls tended to have a shorter duration (8.9 ± 0.3 minutes) than boys (10.6 ± 1.2 minutes), but the difference was not significant.

Heart rate responses: Minute to minute mean heart rates for all groups during and after exercise are shown in Figure 1. All groups showed a similar trend, with an abrupt increase in heart rate during the 1st minute of exercise and a more gradual increase thereafter. The smaller (younger) children had faster heart rates during exercise than did the larger (older) children, but these differences were not significant and disappeared at peak exercise. The mean maximal heart rate for all children was 187 ± 14 beats/min.

Table II lists the heart rates before exercise, at 1 minute of exercise and at peak exercise for the four groups further classified according to sex and race. Heart rates before exercise did not differ significantly within subclasses except between white and black girls in group II. After 1 minute of exercise, girls of both races in group III had significantly faster heart rates than boys of the same group. These differences disappeared at peak exercise.

*With respect to the use of the fourth rather than the fifth Korotkoff sound, reports of studies in adults usually emphasize the fifth Korotkoff sound during exercise. However, in children the fourth and fifth Korotkoff sounds are frequently very close together, or the fifth sound may actually be heard down to 0. This has been emphasized in previous guidelines of the American Academy of Pediatrics by the Task Force on Blood Pressure Control in Children of the National Heart, Lung, and Blood Institute.[13] It is their belief, therefore, that the fourth Korotkoff sound is more representative of diastolic pressure in children.

Blood Pressure, Heart Rate, Pressure-Rate Product and Electrocardiographic Changes in Healthy Children During Treadmill Exercise

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Heart rate, systolic and diastolic blood pressure, rate-pressure product and electrocardiographic changes were measured in 288 healthy children during treadmill exercise. A constant speed (3.5 miles/hour) protocol was used to facilitate the measurements of physiologic data during exercise. Because responses to exercise vary with size, the children were separated into four groups according to body surface area. Comparisons were also made between male and female and between black and white children. The values for heart rate and systolic pressure showed excellent reproducibility in repeated tests. These data establish for clinical use reference values for children during treadmill exercise.

Hemodynamic and cardiopulmonary responses of children to exercise as part of the evaluation of congenital heart lesions have been reported for several years.[1–5] Many of these evaluations were accomplished using a bicycle ergometer, with the child in a supine position in cardiac catheterization laboratories or seated in performance laboratories. The use of exercise tests to evaluate the electrocardiogram, arrhythmias, chest pain, preoperative and postoperative states and hypertension in children has been increasing,[6–8] and the bicycle has been the preferred mode of exercise testing. The advantages of the treadmill as a mode of exercise have been described[9–11]; however, it has been difficult to obtain certain physiologic data from children on the treadmill.

Recently, normal data for healthy children exercised on the treadmill with a variable speed protocol have been published[12]; however, blood pressure responses were not reported. We have obtained physiologic data for healthy black and white children of both sexes during treadmill exercise testing, using a fixed speed protocol that allows measurement of blood pressure as well as the recording of heart rate and electrocardiogram.

Methods

Subjects: Two hundred eighty-eight children with a normal cardiovascular system exercised in the Medical University of South Carolina Pediatric Performance Laboratory. These children had no special athletic ability, body habitus or frequency of activity. The normal population consisted of volunteers and children referred individually for cardiac evaluation because of suspected but not documented arrhythmias, musculoskeletal chest pain or innocent heart murmurs.

There were 119 white male, 59 black male, 66 white female, and 44 black female children and adolescents aged 4 to 21 years. For data analysis the subjects were classified into four groups according to body surface area as follows: Group I (0.72 to 1.09 m^2), 72 subjects; group II (1.10 to 1.39 m^2), 92 subjects; group III (1.40

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laboratory demonstrated in conscious lambs that prostaglandin E_1 affects pulmonary and systemic resistances equally and does not alter the pulmonary to systemic resistance ratio. Therefore, we consider that the predominant effect of prostaglandin E_1 on oxygen tension occurs through its effect on ductal patency.

Potential harmful effects: Ductal dilatation and increased pulmonary blood flow are not entirely beneficial. Treatment with prostaglandin E_1 could precipitate congestive heart failure (Case 8) and therefore should be regarded as a temporary measure preceding an elective Blalock-Hanlon procedure. By supporting the patient with prostaglandin E_1 for several days we had hoped to avoid surgical intervention as the natural decrease in pulmonary vascular resistance occurred. Unfortunately, this was not our experience, and an atrial septectomy (Blalock-Hanlon procedure) was required in all patients. Two patients required prostaglandin E_1 support postoperatively but were successfully weaned from this infusion.

Implications: Infusion of prostaglandin E_1 in d-transposition of the great arteries can result in increased systemic oxygenation after balloon septostomy. Congestive heart failure may complicate therapy. A palliative Blalock-Hanlon operation (atrial septectomy) or, as performed in other centers, an intraatrial baffle procedure can then be arranged on an elective basis, if dependence on prostaglandin E_1 persists.

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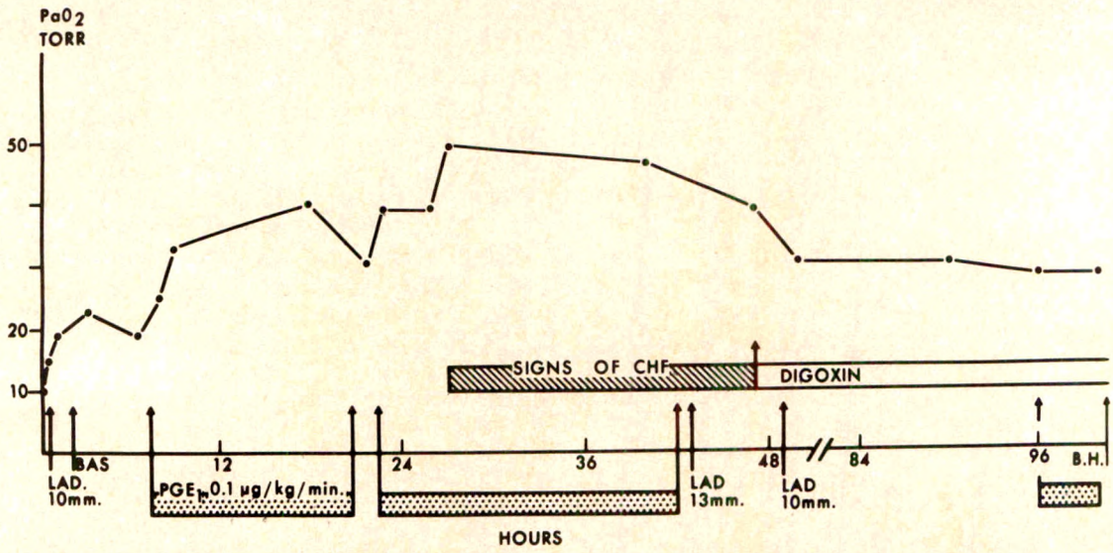

FIGURE 3. Case 8. Changes in arterial partial pressure of oxygen (PaO_2) during discontinuation and reinstitution of prostaglandin E_1 (PGE_1) therapy. Also documented are changes in the left atrial dimension (LAD) as determined echographically. With discontinuation of therapy, the left atrial dimension decreases with the expected decrease in arterial partial pressure of oxygen. BAS = balloon atrial septostomy; B.H. = Blalock-Hanlon procedure; CHF = congestive heart failure.

arteries without pulmonary outflow tract obstruction in whom systemic oxygen saturation after balloon atrial septostomy either was not improved (eight patients) or was decreased after an initial good response (two patients). In the two patients (Cases 2 and 3) who showed no response to prostaglandin E_1, the failure was probably due to (1) short duration of the trial, and (2) inadequate atrial communication.[9] In the patient (Case 6) who had a periappendiceal abscess that required a temporary colostomy, this complication was related to a low-lying arterial catheter rather than to infusion of prostaglandin E_1.[17]

Balloon septostomy: This procedure has improved the 1 month survival rate for patients with d-transposition of the great arteries with or without a ventricular septal defect from 20 percent before 1964 to more than 85 percent.[18] However, aside from a technically poor septostomy, several anatomic[19] and physiologic[5] factors influence the adequacy of atrial mixing.[1] Disappointing clinical responses in patients with a large atrial communication are well documented. These failures may represent a delayed decrease in pulmonary resistance and consequent low pulmonary blood flow[8] with little bidirectional shunting. Balanced ventricular compliances will also decrease mixing during diastole.[7] To lesser degrees, preferential streaming of pulmonary venous return toward the mitral valve and systemic venous return toward the tricuspid valve will also decrease mixing.[8]

Effects of prostaglandin E_1: Ductal dilatation during infusion of prostaglandin E_1 increases total pulmonary blood flow through left to right shunting. Consequently, pulmonary venous return and left atrial pressure are increased, distending the left atrium and encouraging greater left to right intraatrial shunting. The ductal shunt represents increased systemic to pulmonary shunting whereas the increased atrial shunt represents pulmonary to systemic flow. Because the total shunt in either direction must be equal on a minute to minute basis the net result of ductal dilatation is increased mixing between the two circuits. Although atrial pressure could not be measured, echocardiographic left atrial dimensions in Case 8 (Fig. 3) decreased when infusion of prostaglandin E_1 was stopped, and there was an associated decrease in oxygen saturation. The smaller dimensions probably reflected a decreased pulmonary venous return. In a two dimensional echocardiographic study of the results of balloon septostomy, Williams et al.[20] described an infant with oxygen desaturation after septostomy whose condition improved dramatically with infusion of prostaglandin E_1. The atrial septal defect was considered large on echocardiography and found so at intracardiac repair. A beneficial effect of prostaglandin E_1 depends on an adequate atrial communication; otherwise, increasing left atrial pressure would simply close the flat of the septum primum, decreasing mixing and increasing systemic desaturation.

Pulmonary and systemic vascular effects: In experimental animals Cassin et al.[21] demonstrated in a controlled blood flow model that prostaglandin E_1 induces active pulmonary vasodilation. This effect will also increase pulmonary blood flow, especially in neonates whose pulmonary vascular resistance remains elevated. Furthermore, prostaglandin E_1 in small doses has been demonstrated to be a potent systemic arterial vasodilator in most species, including human beings.[22] This alteration in right ventricular afterload would result in a smaller end-diastolic volume and increased left to right shunting at atrial level. Lock et al.[23] in our

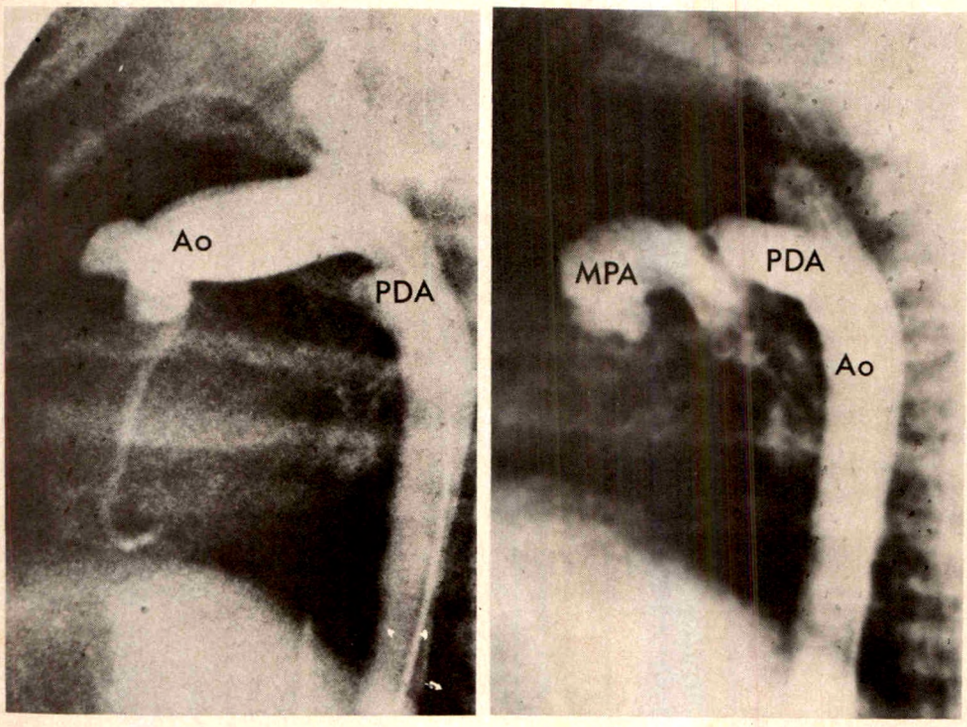

FIGURE 2. Case 6. Aortograms performed in the lateral projection. Injection into the ascending aorta demonstrates the effect of prostaglandin E_1 infusion on ductal patency. **Left,** before infusion; **right,** during infusion. Ao = aorta; MPA = main pulmonary artery; PDA = patent ductus arteriosus.

Congestive heart failure developed in only one patient (Case 8) during the infusion. A Blalock-Hanlon procedure is considered necessary at this institution if the arterial PO_2 cannot be maintained at 30 torr or above. All patients required a Blalock-Hanlon procedure within the first 8 days of life. There were eight survivors, three of whom have had a Mustard intraatrial baffle procedure.

The systemic oxygen saturation before infusion of prostaglandin E_1 was 26 ± 12 percent (mean ± standard deviation) for the entire group and rose to 54 ± 19 percent ($P < 0.01$). The arterial PO_2 before infusion was 17 ± 5 torr and rose to 30 ± 9 torr ($P < 0.001$). In cases 4 and 9, an initial good response to balloon septostomy was achieved. However the arterial PO_2 and systemic oxygen saturation decreased in the intensive care nursery, and on days 3 and 5, respectively, infusion of prostaglandin E_1 was begun. Figure 2 shows the effect of infusion of prostaglandin E_1 on ductal patency in Case 6. Angiographic documentation of ductal dilation was available in one further patient (Case 5). In Cases 1, 5 to 8 and 10 discontinuation of prostaglandin E_1 infusion resulted in a decrease in arterial PO_2 and systemic oxygen saturation to unacceptable levels (less than 30 torr), and a Blalock-Hanlon procedure was required. Figure 3 illustrates in Case 8 these changes as well as a decrease in echocardiographic left atrial dimensions associated with the reduction in systemic oxygen saturation and tension. Patients 6 and 7 required prostaglandin E_1 after the Blalock-Hanlon procedure and were successfully weaned from the agent in the postoperative period.

Two patients died. Patient 5 died suddenly, 5 months after hospitalization without any obvious precipitating event, and Patient 9 died at age 8 days because of overwhelming sepsis 3 days after the Blalock-Hanlon procedure. Unfortunately, the atrial septectomy performed is a closed procedure, and no estimation of the sizes of the balloon septostomy are available.

Minor complications of infusion were a transient fever (Case 10) and cutaneous flushing (Case 7). In Case 6 a periappendiceal abscess developed and a temporary colostomy was required.

Discussion

The value of prostaglandins of the E type in the emergency care of neonates with ductus-dependent congenital heart malformations has been well documented.[9–11] Dilation of the ductus arteriosus in hypoxic neonates with right ventricular outflow tract obstruction increases pulmonary blood flow, reverses hypoxia and allows correction of metabolic acidosis. In infants with aortic arch anomalies, ductal closure compromises adequate systemic flow to the descending aorta, a process that can be reversed with prostaglandin E_1.[15] Increasing ductal flow can also be used to evaluate pulmonary venous pathways and may unmask pulmonary venous obstruction[16] in previously low flow situations. Finally, in patients with inadequate intraatrial mixing after balloon septostomy infusion of prostaglandin E_1 may improve tissue oxygenation.[9–11,14–16]

This report documents the effect of prostaglandin E_1 infusion in 10 neonates with d-transposition of the great

prostaglandin E_1 infusion in d-transposition and discusses possible mechanisms of action.

Methods

The clinical profiles of the 10 newborn infants with d-transposition of the great arteries treated with prostaglandin E_1 are shown in Table I. All underwent diagnostic cardiac catheterization and biplane cineangiography within the first 24 hours of life. A patent ductus arteriosus was present in all, six had an intact ventricular septum and four a small ventricular septal defect. A balloon septostomy was performed, using a no. 4F Rashkind balloon-tipped catheter, through a right saphenofemoral venous cutdown. Arterial saturations were measured before and after septostomy on a Waters oximeter (The Waters Company) or Co-oximeter 1L 82 (Instrumentation Laboratory Inc.).

Prostaglandin E_1 infusion: Prostaglandin E_1 (Upjohn Company) was infused through an umbilical artery in five patients, an umbilical vein in four patients or a peripheral vein in two patients. Patient 3 was given prostaglandin E_1 before balloon septostomy. During catheterization the umbilical arterial catheter used for infusion was positioned just proximal to the ductus arteriosus, while venous lines were situated at the right atrial-inferior vena caval junction. Prostaglandin E_1 (0.5 mg. in 1.0 ml ethanol diluted in a solution of two thirds dextrose and one third sodium chloride to a concentration of 0.4 mg/ml) was infused in a test dose of 0.1 μg/kg per min using a Harvard constant infusion pump. To decrease fluid load, the dose was subsequently decreased to 0.05 μg/kg per min and, provided adequate arterial partial pressure of oxygen (PO_2) and oxygen saturation were maintained, that dose was continued. Arterial blood gases were obtained at 4 to 6 hour intervals from right brachial or radial artery punctures and measured on a Radiometer (BMF3MK2) Blood micro system. Respiratory rate, heart rate and blood pressure were monitored and any side effects such as pyrexia, hypotension, bradycardia, muscle twitching or apneic spells noted. Statistics were analyzed using the two-tailed Student's *t* test.

Results

The changes in arterial oxygen saturations and pressures during treatment with prostaglandin E_1 are shown in Figure 1. In eight patients the infusions were continued from 3 hours to 312 hours (mean 98 hours).

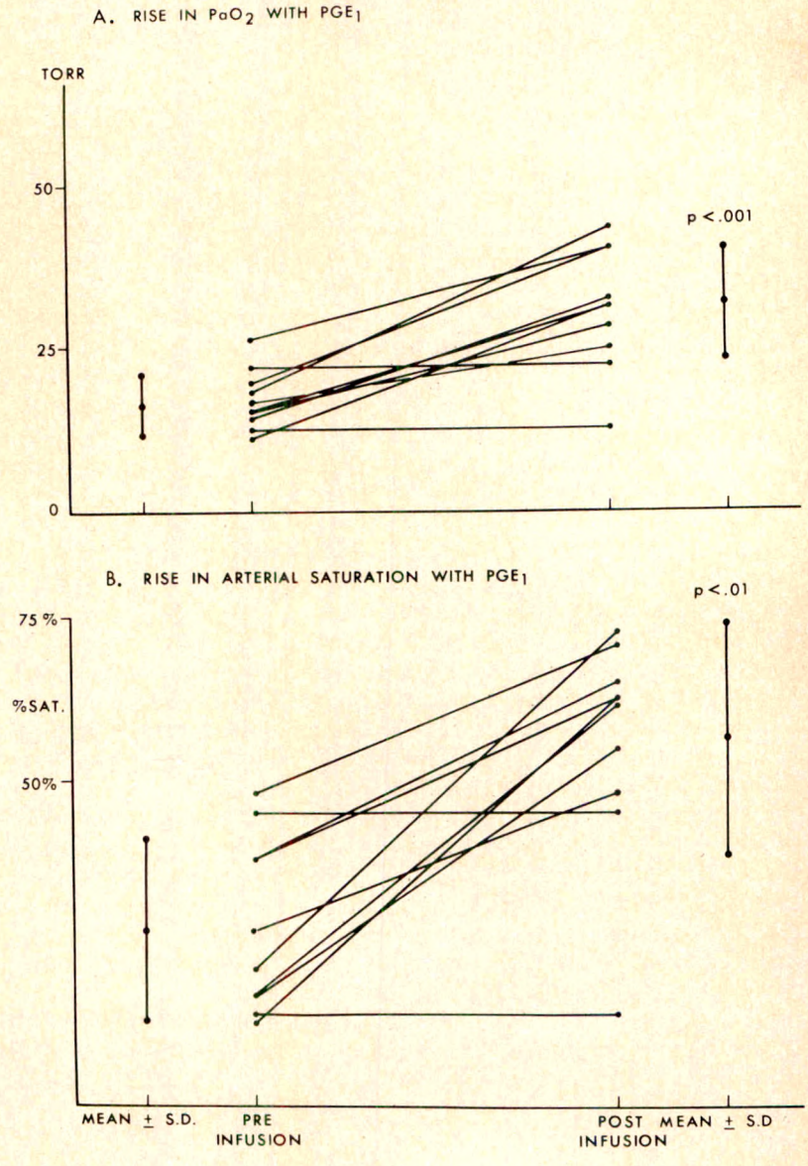

FIGURE 1. Changes in arterial partial pressure of oxygen (**A**) and oxygen saturation (**B**) before and after infusion of prostaglandin E_1 (PGE_1). Two children demonstrated no response; one of these had the infusion before septostomy. Probability (p) values indicating the significance of differences in values before and after infusion are indicated. PaO_2 = arterial partial pressure of oxygen; POST = after infusion; PRE = before infusion; SAT. = saturation; S.D. = standard deviation.

TABLE I

Clinical Data

Case no.	Sex	Diagnosis	PGE_1 Infusion			PaO_2 (SaO_2)			Outcome	Complications
			Duration	Route	Dose (μg/kg per min)	Pre Septostomy	Post Septostomy	During PGE_1 Infusion		
1	M	d-TGA, PDA, IVS	48 hr	UV	0.1–0.05	26 (52)	15 (38)	28 (65)	B-H @ 2 days; home	None
2	M	d-TGA, PDA, IVS	5 min	UA	0.1	22 (34)	22 (34)	22 (34)	B-H @ 2 days; home	None
3*	M	d-TGA, PDA, IVS	10 min	UA	0.1	12 (14)	12 (14)	12 (14)	B-H @ 2 days; Mustard @ 1 yr; home	None
4†	M	d-TGA, PDA, IVS	3 hr	IV	0.1	16 (15)	11 (13)	31 (63)	B-H @ 72 hours; Mustard @ 1 year; home	None
5	M	d-TGA, PDA, IVS	4 hr	UA	0.08	18 (33)	26 (48)	40 (71)	B-H @ 2 days; died at home @ 5 mo	None
6	M	d-TGA, PDA, VSD	13 days	UA‡ IV	0.05–0.025	15 (38)	15 (38)	31 (63)	B-H @ 8 days; PGE_1 cont. 4 days postop; home	Appendiceal abscess
7	M	d-TGA, PDA, IVS	5 days	UA	0.1	. . . (42)	18 (21)	43 (73)	B-H @ 24 hr; PGE_1 given postop; Mustard 2 mo; home	Rash
8	F	d-TGA, PDA, VSD	6 days	UV	0.1	14 (15)	19 (17)	40 (62)	B-H @ 6 days; home	None
9†	F	d-TGA, PDA, IVS	3 days	UV	0.1	26 (54)	14 (17)	32 (55)	B-H @ 5 days; died	Sepsis
10	F	d-TGA, PDA, mild subvalve PS	24 hr	UV	0.1	19 (26)	19 (26)	25 (37)	B-H @ 2 days	Transient fever

* Patient 3 had the infusion before balloon septostomy.

† Patients 4 and 9 had initial good results from the Rashkind procedure. However, decreasing PaO_2 (SaO_2) in the intensive care nursery resulted in the prostaglandin E_1 infusion.

‡ Patient 6 had the umbilical arterial catheter removed and received prostaglandin E_1 intravenously when signs of intraabdominal disease occurred.

B-H = Blalock-Hanlon procedure; cont. = continued; d-TGA = d-transposition of the great arteries; IV = peripheral intravenous; IVS = intact ventricular septum; PaO_2 = arterial partial pressure of oxygen (torr); PDA = patent ductus arteriosus; PGE_1 = prostaglandin E_1; postop = postoperatively; SaO_2 = arterial oxygen saturation (%); subvalve PS = subvalve pulmonary stenosis; UA = umbilical artery; UV = umbilical vein; VSD = ventricular septal defect.

Role of Prostaglandin E_1 Infusion in the Management of Transposition of the Great Arteries

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That prostaglandin E_1 can produce an increase in systemic oxygen saturation in patients with cyanotic heart disease and ductus dependent pulmonary blood flow has been well documented. However, its use in complete transposition to increase systemic oxygen saturation by increasing mixing has not been well investigated. Ten newborn infants with angiographic diagnosis of d-transposition of the great arteries and patent ductus arteriosus were studied; 6 had an intact ventricular septum. Prostaglandin E_1 infusion (0.1 μg/kg per min) was started after balloon atrial septostomy because of a persistently low systemic oxygen saturation of 26 $\pm$ 12 percent (mean $\pm$ standard deviation) and oxygen tension of 17 $\pm$ 5 torr. The infusion resulted in an increase in systemic oxygen saturation to 53 $\pm$ 19 percent ($P < 0.01$) and oxygen tension to 30 $\pm$ 9 torr ($P < 0.001$). In 2 of 10 patients, there was no increase in systemic oxygen saturation with the infusion (1 had the infusion before the septostomy and both had the infusion for less than 10 minutes). In 8 of 10 patients, the infusion was continued from 4 to 312 hours (average 98 hours) until a Blalock-Hanlon procedure was performed. Two babies became septic, and one of them died. A third had a transient fever. All children whose prostaglandin E_1 infusion was discontinued before atrial septectomy had a reduction in systemic oxygen saturation to unacceptable levels. Two patients who required infusion (for 5 days) after septectomy were successfully weaned from the drug.

It is concluded that dilation of the ductus by prostaglandin E_1 infusion increases pulmonary blood flow (left to right shunt) which in turn favorably influences atrial mixing (left to right shunt) and increases systemic oxygen saturation. Pulmonary blood flow may be further increased by a decrease in pulmonary vascular resistance induced by prostaglandin E_1.

Survival of infants with d-transposition of the great arteries requires adequate intracardiac mixing between the systemic and pulmonary circulations, which is usually ensured by a balloon atrial septostomy.[1] Frequently the systemic oxygen saturation level rises initially after septostomy but then falls to unacceptable levels within hours. These children must then undergo a semi-urgent Blalock-Hanlon[2] or Mustard's operation.[3]

A poor response to septostomy may reflect a technically inadequate procedure[4] with only dilatation of the foramen ovale or it may result from a variety of other factors[5–8] when an adequate septostomy has been achieved. Prostaglandin E_1 augments pulmonary blood flow in children with cyanotic heart disease[9–11] and increases systemic oxygen saturation, both by ductal enlargement and perhaps by decreasing pulmonary vascular resistance.[12,13] Neutze et al.[14] and Olley and colleagues[9] have reported the effect of prostaglandin E_1 infusion in eight patients with d-transposition of great arteries after balloon septostomy. This report documents our further experience at the Hospital for Sick Children with

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management of symptomatic infants with coarctation of the aorta is associated with a high mortality rate.[2] Previous experience with end to end anastomosis has also been associated with a high mortality rate and a high incidence rate of recoarctation.[12–14] Our results demonstrate that repair of coarctation of the aorta can be undertaken in infants with other anomalies, with a mortality risk of less than 10 percent. Factors that influence mortality in infants include correction of metabolic acidosis, treatment with digoxin and diuretic agents, careful maintenance of normothermia and postoperative ventilatory support. In addition, our group believes that aortoplasty performed to relieve all obstruction is of major importance in decreasing mortality.

Pulmonary arterial banding before repair of coarctation has been advocated by Connors et al.,[8] but we believe that pulmonary arterial banding should be deferred until after repair of the coarctation. This sequence allows intracardiac hemodynamics to equilibrate before banding. Nine of 17 patients (53 percent) with ventricular septal defect required pulmonary arterial banding. This proportion is greater than the 28 percent reported by Connors et al.[8]

Operative mortality and follow-up results of aortoplasty: In a study by Macmanus et al.[11] of 44 infants who underwent end to end repair of coarctation at less than age 3 months, there was an operative mortality rate of 32 percent. Furthermore, only 8 of 17 survivors (47 percent) had a blood pressure gradient of less than 20 mm Hg at the repair site after a mean follow-up period of 4.2 years. Although long-term follow-up data are not available regarding recoarctation after aortoplasty, early results are encouraging.[14,15] Aortoplasty is our technique of choice for repair of coarctation of the thoracic aorta in small children because we anticipate a decreased incidence of recoarctation.

Possible aneurysm formation: The bulge resulting from patch aortoplasty is evident in the posteroanterior chest X-ray film (Fig. 3). Although Dacron has proved a satisfactory arterial graft material in adults for up to 20 years, the long-term results in children require continuing evaluation. Although there have been scattered reports of aneurysm formation after Dacron repair of coarctation of the aorta, these cases appear to be related to technical difficulties or infection[16,17]; however, ongoing long-term evaluation is mandatory for this group of patients.

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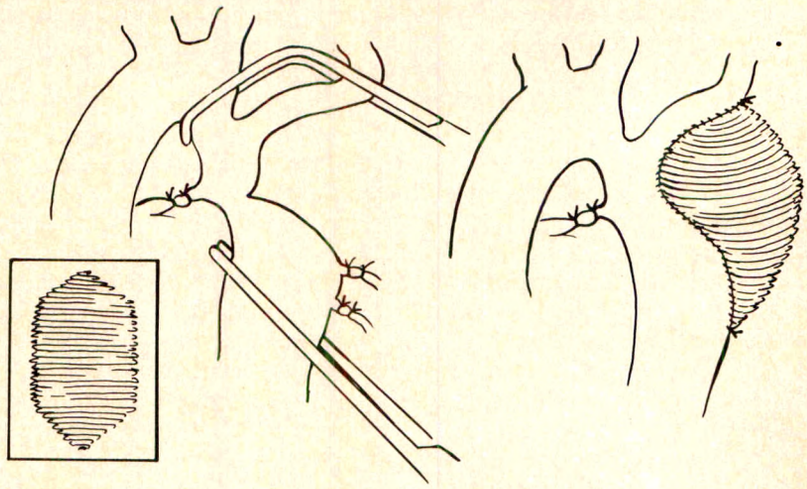

FIGURE 1. Surgical procedure. **Left,** clamps on vessels. **Right,** completed patch.

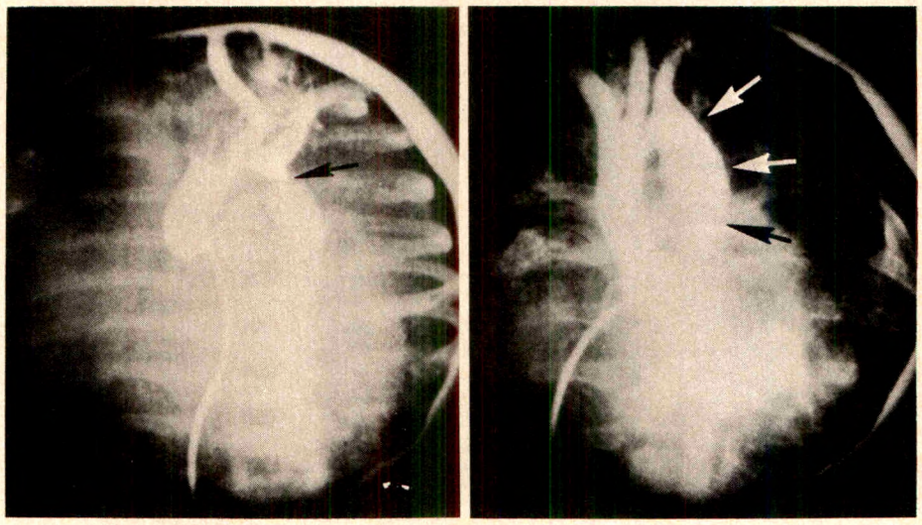

FIGURE 2. Angiograms. **Left,** preoperative, showing the coarcted segment (**arrow**) with the pulmonary artery faintly opacified through the ductus. **Right,** 8 months postoperative. Note the bulge at the site of the patch (**white arrows**) and extension of the patch onto the left subclavian artery.

Results

All patients survived surgical repair and demonstrated clinical lessening of congestive heart failure. Twenty-two of 23 patients (96 percent) were discharged from the hospital 7 to 74 days after operation. One patient (Case 22) died 42 days postoperatively of a bowel perforation and sepsis. Postoperative hospitalization beyond 21 days was necessary only in patients with other congenital cardiac anomalies. There were three late deaths (Table III).

Fourteen patients had cardiac catheterization 6 to 15 months after repair of coarctation (Fig. 2). No gradients were found at the site of coarctation repair, but in one infant there was a 10 mm Hg gradient across the transverse aortic arch.

Discussion

Coarctation repair in early infancy: We believe patch aortoplasty can be safely offered to infants with critical coarctation of the aorta despite the nearly universal presence of other cardiac anomalies. Medical

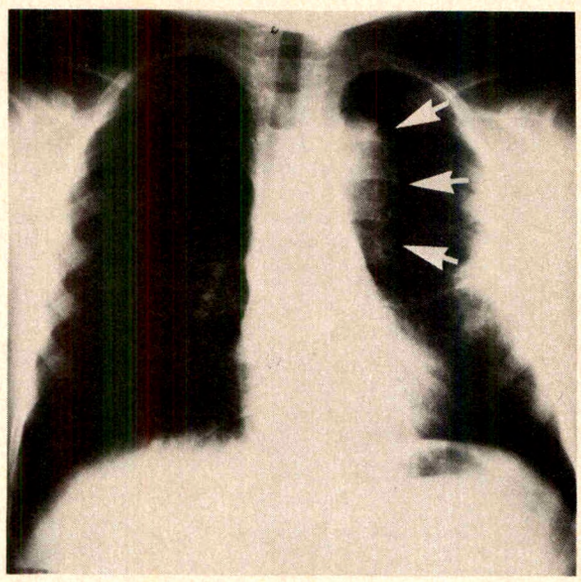

FIGURE 3. Postoperative chest X-ray film. Note the large bulge at the site of repair.

TABLE I

Reported Surgical Mortality Rates for Surgical Repair of Coarctation of Aorta in Infants

Year	First Author	Patients (no.)	Operative Mortality (%)	Age at Operation
1959	Mortensen[2] (collected cases)	65	37	< 1 yr
1959	Mortensen[2]	8	0	< 1 yr
1960	Glass[4]	34	41	< 1 yr
1969	Tawes[5]	123	58	< 3 yr
1971	Litwin[6]	46	30	< 2 yr
1974	Reul[7]	19	26	< 2 yr
1976	Connors[8]	18	17	< 1 yr
1976	Fishman[9]	22	14	< 3 mo
1976	Chiariello[10]	21	57	< 3 mo
1977	Macmanus[11]	44	32	< 3 mo
1978	Fleming (present series)	23	0	< 3 mo

TABLE II

Diagnosis and Surgical Treatment of Lesions Associated With Coarctation of Aorta in 23 Infants

Case no.	Age at Catheterization (days)	Age at Operation (days)	Associated Lesions	Repair in Addition to Aortoplasty
1	41	48	PDA, VSD, LV dysfunction	Lig PDA
2	49	50	VSD (small)	
3	52	59	PDA, ASD, VSD, multiple hemangiomas	Lig PDA, PA band
4	47	48	PDA, ASD, TGV, common ventricle, single A-V valve	Lig PDA, PA band
5	10	10	PDA, VSD	Lig PDA
6	8	11	PDA, VSD	Lig PDA
7	10	11	PDA, VSD (small)	Lig PDA
8	25	29	VSD	
9	76	78	LV dysfunction, mitral stenosis	
10	33	38	Endocardial cushion defect with mitral regurgitation	
11	28	28	PDA, VSD	Lig PDA, PA band
12	8	10	PDA, mitral atresia, hypoplastic LA, hypoplastic LV, DORV, S/p B-H	Lig PDA, PA band
13	33	39	PDA, VSD, TGV, S/p B-H	Lig PDA, PA band
14	4	9	PDA, ASD, VSD, corrected TGV, dextrocardia	Lig PDA, PA band
15	60	60	PDA, RV outflow obstruction	Lig PDA
16	84	87	PDA	Lig PDA
17	10	10	PDA, VSD	Lig PDA
18	14	15	PDA, VSD	Lig PDA, PA band
19	3	4	PDA	Lig PDA
20	10	11	PDA, VSD	Lig PDA, PA band
21	18	18	PDA, VSD	Lig PDA
22	1	4	PDA, TGV, VSD, S/p B-H	Lig PDA, PA band
23	7	7	PDA, VSD (small)	Lig PDA

ASD = atrial septal defect; A-V = atrioventricular; band = banding; DORV = double outlet right ventricle; LA = left atrium; Lig = ligation; LV = left ventricular; PA = pulmonary artery; PDA = patent ductus arteriosus; RV = right ventricular; S/p B-H = status post Blalock-Hanlon septectomy; TGV = transposition of the great vessels; VSD = ventricular septal defect.

anomaly (Table II). All patients underwent surgical repair of coarctation within 7 days of initial diagnostic study. In three patients, repair of coarctation followed a Blalock-Hanlon atrial septectomy by 2 to 4 days (Case 11, 12 and 22).

Surgical technique: Operations were performed under light general endotracheal anesthesia with muscle relaxants, which were not pharmacologically reversed after the procedure. All operations were performed through a left posterolateral thoracotomy, with opening of either the third or fourth intercostal space. After the vessels involved were dissected, the ductus arteriosus was closed with two or three ligatures.

The coarcted segment of the aorta was then controlled with vascular clamps (Fig. 1, left); the aorta was opened longitudinally, and any membrane present was excised. The aortotomy was extended from the inferior portion of the left subclavian artery to the largest portion of the descending aorta. A patch of preclotted knitted Dacron®, cut from Dacron tubing (diameter 12 to 20 mm), was used to create a luminal diameter of at least 16 mm (Fig. 1, right). Aortic cross-clamp time was 20 to 30 minutes. The distal clamp was removed first, and the proximal clamp released slowly to avoid a precipitous decrease in blood pressure.

This technique is similar to those described by Moor[15] and Reul[7] and their co-workers. We have modified the technique by using a patch of larger diameter and extending it farther distally on the left subclavian artery to provide a large lumen in an attempt to minimize the chance of recoarctation.

When the patient's condition had stabilized after this portion of the procedure, patients with a ventricular septal defect had their aortic and pulmonary arterial pressures measured directly. If the pulmonary artery/aortic pressure ratio was greater than 0.67, the pulmonary artery was banded to achieve a pressure ratio of approximately 0.50. Nine of the 17 patients with a ventricular septal defect (53 percent) had pulmonary arterial banding.

Postoperative management: All patients were returned to the pediatric intensive care unit. They were treated with volume respirators, intermittent mandatory ventilation and continuous positive airway pressure. Patients remained intubated until the effects of muscle relaxant were no longer evident. Extubation was accomplished 18 to 24 hours after operation.

TABLE III

Deaths in Infants Undergoing Aortoplasty for Coarctation of Aorta

Case no.*	Time Post-Repair (CoA)	Associated Lesions	Cause of Death
22	42 days	PDA, TGV, VSD	Bowel perforation and sepsis
10	3 mo	Endocardial cushion defect, severe mitral regurgitation	Died at time of operation for repair of mitral valve and ASD closure
3	9 mo	ASD, VSD	Infected hemangiomas of face. Sepsis unrecognized at home until patient was moribund
4	18 mo	ASD, TGV, common ventricle, single A-V valve with valve regurgitation	Low output failure secondary to severe heart disease

* Refer to Table II.

ASD = atrial septal defect; A-V = atrioventricular; CoA = coarctation of aorta; PDA = patent ductus arteriosus; TGV = transposition of the great vessels; VSD = ventricular septal defect.

Critical Aortic Coarctation: Patch Aortoplasty in Infants Less Than Age 3 Months

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Omaha, Nebraska

Twenty-three infants less than age 3 months (mean age 31 days) underwent patch aortoplasty for relief of coarctation of the aorta. All had intractable congestive heart failure, despite aggressive medical therapy. Each infant had other cardiac anomalies, including patent ductus arteriosus (83 percent) and ventricular septal defect (74 percent). All patients underwent closure of the ductus arteriosus and patch angioplasty of the aorta to produce a luminal diameter of at least 16 mm. In addition, 9 of the 17 patients (53 percent) with a large shunt ventricular septal defect underwent pulmonary arterial banding. There was one hospital death 42 days after operation secondary to bowel perforation and sepsis. Hospitalization beyond 21 days postoperatively was always due to other unrepaired cardiac lesions. The three late deaths at 3, 9 and 18 months after operation were associated with additional major anomalies. Fourteen patients have had postoperative catheterization. No gradient was found across the site of coarctation repair, but one patient had a gradient between the left carotid and left subclavian arteries. Surgical repair of critical coarctation of the aorta in infants can safely be offered despite the presence of other cardiac anomalies.

Infants with coarctation of the aorta presenting with congestive heart failure are usually difficult to manage. Coarctation is one of the major causes of congestive heart failure within the 1st month of life, especially if associated with other cardiac anomalies. Many infants may not survive without early operation.[1–3] Early operation for coarctation has been accompanied by a high mortality rate ranging from 17 to 57 percent (Table I).[4–11] Recoarctation is a recognized complication for survivors of coarctation repair by end to end anastomosis especially when operation is performed early in life.[12–14] Therefore, we are reporting our experience with patch repair of coarctation in early infancy.

Methods

Patients studied: During a 3 year period ending October 1, 1978, 23 infants under age 3 months had surgical repair of coarctation of the aorta at Henrietta Egleston Hospital for Children in Atlanta, Georgia or at the University of Nebraska Medical Center in Omaha, Nebraska. There were 16 male and 7 female infants whose weight ranged from 2,009 to 4,172 g (mean 3,103) at operation.

Preoperative evaluation and management: Signs and symptoms of moderate to severe congestive heart failure continued in all patients despite treatment with diuretic agents, digoxin and salt restriction. All patients underwent cardiac catheterization within 7 days of initial presentation. Data obtained included intracardiac pressure assessment and angiographic visualization of the aorta. All patients had a measured pulmonary arterial pressure greater than 50 mm Hg, consistent with pulmonary hypertension. Discrete stenosis of the descending aorta distal to the left subclavian artery was observed on angiography. In 17 patients (74 percent) the descending aorta filled at least partially through a patent ductus arteriosus. Each patient had at least one associated cardiac

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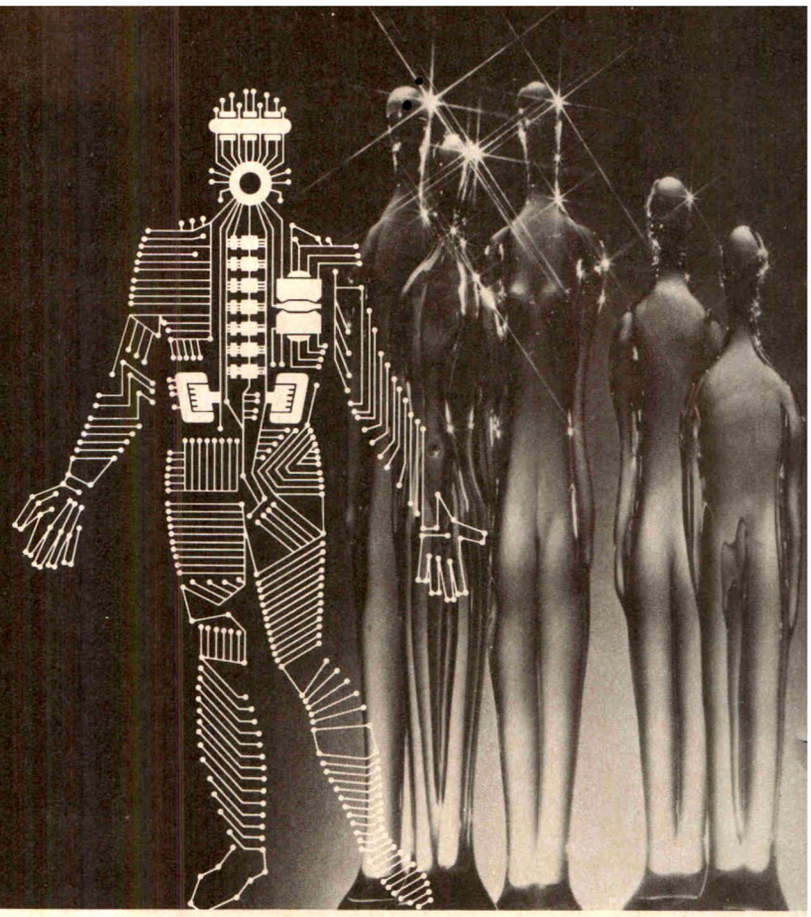

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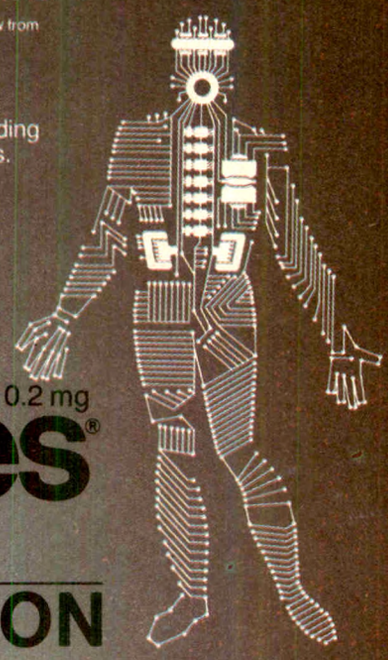

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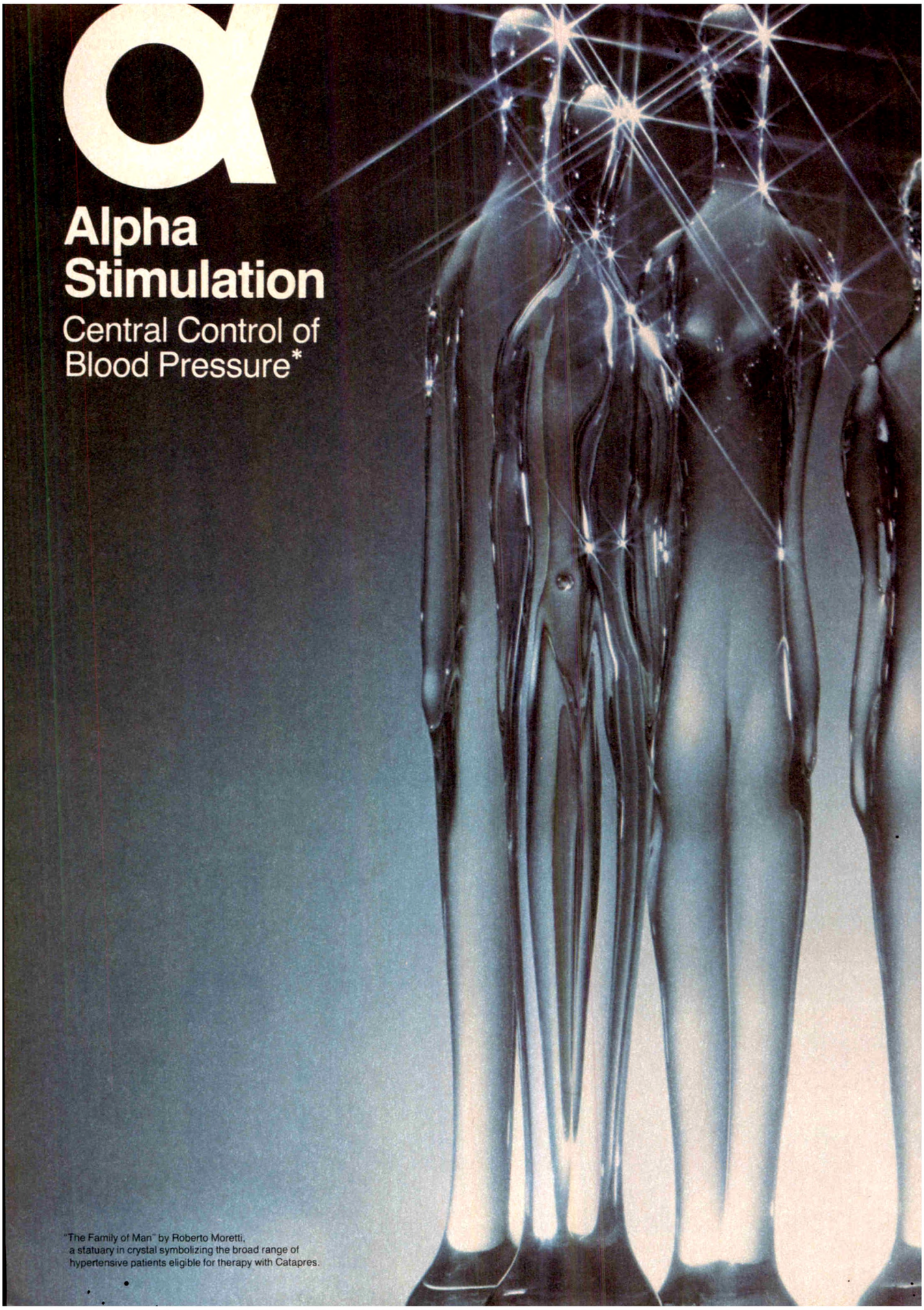
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Injection penicillin G benzathine is the recommended drug of choice* to prevent streptococcal infection and possible recurrence of rheumatic fever. One injection, once a month, of 1,200,000 units usually offers effective and continuous prophylaxis, virtually eliminating the problem of patient compliance.

*Commission on Rheumatic Fever and Bacterial Endocarditis of the Council on Cardiovascular Disease in the Young: "Rheumatic Fever Prevention," 71-006-B. American Heart Association, New York, (Sept.) 1976.

INJECTION

BICILLIN® L-A

(STERILE PENICILLIN G BENZATHINE SUSPENSION)

Wyeth Laboratories
Philadelphia, Pa. 19101

◀ See important information on preceding page.

Give your patients the KLORVESS® sparkle

Klorvess® Effervescent Granules and Klorvess® (potassium chloride) 10% Liquid

Brief summary of prescribing information

DESCRIPTION: *Klorvess Effervescent Granules:* Each packet (2.8 g) contains 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, L-lysine monohydrochloride 0.913 g in a sodium-, sugar- and carbohydrate-free effervescent formulation. Dissolution of the packet contents in water provides the potassium and chloride available for oral ingestion as potassium chloride, potassium bicarbonate, potassium citrate and L-lysine monohydrochloride.

Klorvess (potassium chloride) 10% Liquid: Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

INDICATIONS: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

CONTRAINDICATIONS: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

PRECAUTIONS: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements. Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis. High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest. To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve the packet contents of *Klorvess Effervescent Granules* in 3 to 4 ounces of cold water, fruit juice or other liquid or dilute each tablespoonful of *Klorvess (potassium chloride) 10% Liquid* in 3 to 4 ounces of cold water. Both of these solutions should be ingested slowly with or immediately after meals.

ADVERSE REACTIONS: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts. The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest. The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

DOSAGE AND ADMINISTRATION: *Klorvess Effervescent Granules:* Adults—One packet completely dissolved 2 to 4 times daily depending upon the requirements of the patient.

Klorvess (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) completely diluted in cold water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating.

OVERDOSAGE: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

HOW SUPPLIED: *Klorvess Effervescent Granules*—packages of 30 packets (2.8 g each). *Klorvess (potassium chloride) 10% Liquid* (dark red)—as a cherry-with-pit flavored liquid in pint and gallon bottles. Klorvess Effervescent Granules and Liquid are also available in institutional packaging as follows: *Klorvess Effervescent Granules*—packages of 1000 packets; *Klorvess Liquid*—36 (3 x 12) x 4 oz Unit-of-Use bottles and 100 (4 x 25) x 15 ml Unit-Dose bottles.

(For complete details, please consult full prescribing information)

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FOR DEEP INTRAMUSCULAR INJECTION ONLY.

Indications: In treatment of infections due to penicillin G-sensitive microorganisms susceptible to the low and very prolonged serum levels common to this dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and clinical response.

The following infections usually respond to adequate dosage of IM penicillin G benzathine.

Streptococcal infections (Group A—without bacteremia). Mild to moderate upper respiratory infections (e.g., pharyngitis).

Venereal infections —Syphilis, yaws, bejel, and pinta.

Medical conditions in which penicillin G benzathine therapy is indicated as prophylaxis:

Rheumatic fever and/or chorea —Prophylaxis with penicillin G benzathine has proven effective in preventing recurrence of these conditions. It has also been used as followup prophylactic therapy for rheumatic heart disease and acute glomerulonephritis.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens. Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

In streptococcal infections, therapy must be sufficient to eliminate the organism, otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of non-susceptible organisms including fungi. Take appropriate measures if superinfection occurs.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness-like reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high parenteral doses.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Composition: (units penicillin G benzathine as active ingredient in aqueous suspension): 300,000 units per ml—10-ml multi-dose vial. Each ml also contains sodium citrate buffer, approximately 6 mg lecithin, 3 mg povidone, 1 mg carboxymethylcellulose, 0.5 mg sorbitan monopalmitate, 0.5 mg polyoxyethylene sorbitan monopalmitate, 1.2 mg methylparaben and 0.14 mg propylparaben.

600,000 units in 1-ml TUBEX® (sterile cartridge-needle unit) Wyeth, packages of 10.

900,000 units, 1.5-ml fill in 2-ml TUBEX, packages of 10.

1,200,000 units in 2-ml TUBEX, packages of 10, and in 2-ml single-dose disposable syringe, packages of 10.

2,400,000 units in 4-ml single-dose disposable syringe, packages of 10.

Each TUBEX or disposable syringe also contains sodium citrate buffer and, as w/v, approximately 0.5% lecithin, 0.6% carboxymethylcellulose, 0.6% povidone, 0.1% methylparaben and 0.01% propylparaben.

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INJECTION
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(STERILE PENICILLIN G BENZATHINE SUSPENSION)

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- sugar, sodium, carbohydrate and dye free
- each packet delivers 20 mEq of potassium and chloride
- convenient packets are easy to carry in patient's pocket or purse
- mix with water or juice for pleasant daily dosage

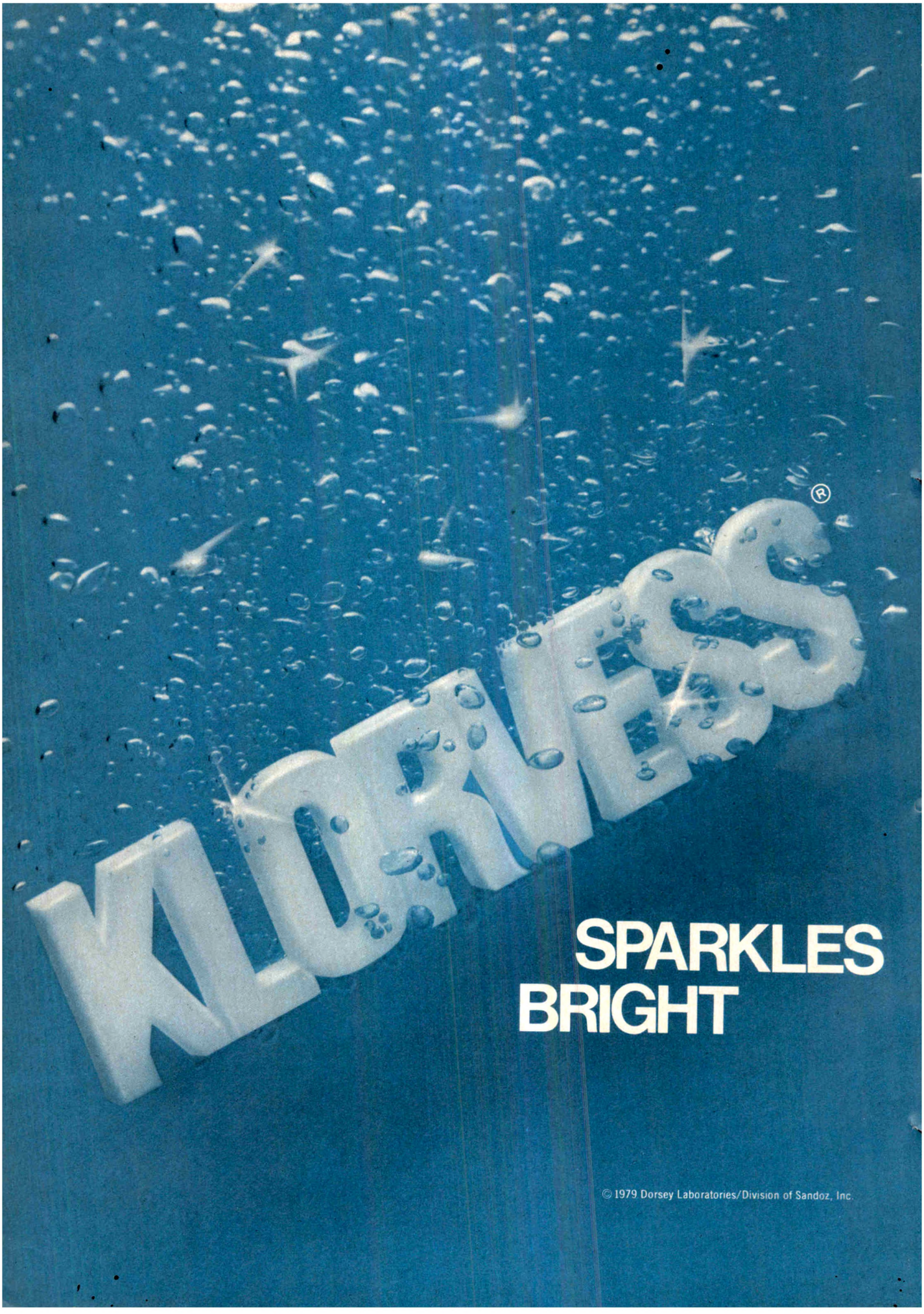
KLORVESS® (potassium chloride) **10% LIQUID** offers sparkling good taste for greater patient compliance. Delicious cherry-with-pit flavor, and 20 mEq of potassium chloride in each dose (15 ml), alcohol 1%.

Give your patients the KLORVESS sparkle

Please see brief summary of prescribing information on adjoining page.

21790

*U.S. Patent No. 4,093,710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tain and less expensive than myocardial scintigraphy. The electrocardiogram, conventional serum enzyme measurements and myocardial scintigrams were useful adjuncts in this study, the latter only in comparison with a preoperative control image. Although no overlap was found using CK-MB to identify patients with perioperative infarction in this study, the presence of additional positive tests strengthens the diagnosis of perioperative myocardial infarction.

Acknowledgment

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a rapid and practical means not only for identifying perioperative myocardial infarction but also for gathering information regarding the magnitude of the injury.

SGOT and LDH isoenzyme values were less sensitive and specific in detecting perioperative myocardial infarction because of concomitant skeletal muscle injury and hemolysis. For this reason, only those patients with an SGOT level greater than 90 IU or LDH_1 isoenzyme greater than LDH_2 isoenzyme, or both, were considered to have enzyme values indicative of perioperative myocardial infarction. False positive LDH isoenzyme values, likely due to hemolysis, occurred in only two patients.

When defining the incidence of perioperative myocardial infarction, it is important to use a precise, quantitative method of CK-MB analysis and to confine the study group to those patients receiving only coronary bypass surgery. Electrophoresis and fluorometric scanning, as previously reported,[9,10,15,17–19,22] may not be as precise and sensitive as necessary, especially in the surgical patient, in whom the MB-MM ratio may be low because of liberation of large amounts of CK-MM from skeletal muscle injury.[33] This may be one reason that CK-MB analysis was found to be only of limited value for defining perioperative myocardial infarction in several previous reports.[14,15,18,20] We have defined the upper limits of "normal" for perioperative CK-MB in patients receiving only isolated coronary bypass surgery, and results should not be compared with those in series in which patients with surgery for valvular and congenital heart disease were included.[8,14,18,19–22] In such patients a much wider range of CK-MB values might be expected.

In patients with perioperative myocardial infarction peak levels of CK-MB and the disappearance of CK-MB were delayed when compared with control values and those in patients without perioperative myocardial infarction. Peak CK-MB occurred at an average interval of 9.2 ± 5.8 (standard deviation) hours after operation in patients with perioperative myocardial infarction compared with only 4.7 ± 3.3 hours in patients without this complication ($P < 0.001$). This suggests that direct surgical trauma produces immediate short-term liberation of the enzyme into the circulation whereas perioperative necrosis with reperfusion results in more prolonged and slower release of CK-MB.

Correlation of CK-MB and new Q waves: In every instance, patients with new Q waves (equal to or greater than 0.04 second) in the postoperative period had other confirmatory evidence of myocardial infarction, and serum CK-MB levels were strikingly elevated in all eight patients with this electrocardiographic pattern and were similar to values observed in acute myocardial infarction in nonsurgical patients.[34] This finding supports the specificity of new Q waves as reported by others[16,17,19] and is in contrast to a recent report.[44] However, accepting only new Q waves as evidence for perioperative myocardial infarction would underestimate the true incidence of such an event.[45,46] Nontransmural myocardial infarction was suspected in five patients because of elevated CK-MB values and each had other evidence of myocardial necrosis as well. Despite its reported limitations, when used in the manner reported herein, the electrocardiogram was quite specific and sensitive. Only five false positive and two false negative tracings could be found in this study.

Correlation of CK-MB with myocardial scintigraphy: Technetium-99m scintigraphy proved to be a useful addition to electrocardiography and enzyme analysis. However, it might not be as sensitive and specific for detection of subendocardial myocardial infarction as initially thought.[23–31] Difficulty in interpretation was presented primarily by the grade 2 diffuse pattern,[23–27,47,48] which we observed preoperatively in five patients. No new diffuse patterns were seen after operation. The scintigram gave negative results in two patients with perioperative myocardial infarction (Table II); thus, a negative image should not exclude the diagnosis of myocardial infarction in the presence of high CK-MB values suggestive of myocardial injury. If scintigraphy is to be used for detection of perioperative myocardial infarction, a preoperative study should be available for comparison as the image may be positive preoperatively. This has been attributed, on occasion, to unstable angina, a recent myocardial infarction or a ventricular aneurysm.[23–28] Five of the 65 patients tested with scintigraphy had a positive image preoperatively. All five had either a myocardial infarction within 1 year before operation or unstable angina. Three of those five scintigrams became negative in the postoperative period, a phenomenon that has been observed previously.[21] However, CK-MB is not likely to be elevated before operation in patients with angina or myocardial ischemia, and elevation of CK-MB suggests myocardial necrosis.[34]

Clinical significance of perioperative infarction: Perioperative myocardial infarction may have serious consequences. It seems reasonable that loss of myocardium may contribute to the impaired or unimproved left ventricular function often reported after operation.[16,49] Both patients who did not survive surgery could not be weaned from cardiopulmonary bypass and had scattered areas of early myocardial injury at autopsy. Although the diagnosis of perioperative myocardial infarction could not be made with certainty because of the short time interval between surgery and death, it seems likely that operative ischemic injury contributed to the postoperative myocardial failure. The other 13 patients did not have any major detectable postoperative complications. The long-term consequences of perioperative myocardial infarction in these patients cannot be assessed at the present time.

Implications: The results of our study indicate that quantitative CK-MB analysis by column chromatography is an important and valuable tool for assessing myocardial necrosis in the early postoperative period. It alerts the clinician to the possibility of postoperative complications in patients with high enzyme values. A single determination of CK-MB obtained 6 to 12 hours after operation may be sufficient and it is easier to ob-

liter only at 6 hours after operation. The highest individual values for CK-MB peak and CK-MB release in the control group were 20 IU/liter (mean 13.1 ± 5.1) and 438 IU/liter (mean 294 ± 97), respectively (Table I).

Correlation of CK-MB activity and electrocardiographic changes: Although there was general agreement among mean values of CK-MB peak levels, mean values of estimated CK-MB release and electrocardiographic patterns, there were discrepancies in individual patients (Table II). All patients with new Q waves (group I) had peak and total CK-MB values well above those of the control group, thus confirming the electrocardiographic diagnosis of perioperative myocardial infarction. Patients in both electrocardiographic groups II and III could be classified into two subsets. A total of 87 patients, 82 of 84 in group III and 5 of 8 in group II, had CK-MB values similar to those of the control group. However, CK-MB values from the remaining five patients in those two groups were similar to values obtained in group I, suggesting the occurrence of perioperative myocardial infarction. On the basis of CK-MB analysis, perioperative myocardial infarction could be excluded in 87 patients because their CK-MB values were all within the range of the control group (or within mean + 2 standard deviations) whereas 13 patients had sustained a perioperative myocardial infarction as defined by values for peak CK-MB and CK-MB release exceeding the values of the control group.

Correlation of CK-MB, SGOT and LDH isoenzyme activity: CK-MB analysis in the period after operation was further evaluated by comparison with results obtained from measurements of SGOT and LDH isoenzyme activity and scintigraphy (Table II). All 13 patients with CK-MB criteria of perioperative myocardial infarction had at least two additional tests consistent with myocardial necrosis whereas the other 87 patients did not have perioperative myocardial infarction by this analysis. In 4 of these 13 patients either the LDH isoenzyme or SGOT values remained within our defined limits; however, these data were considered false positive in two and three patients, respectively, who had no perioperative myocardial infarction. Table II supports the previous classification of electrocardiographic groups II and III into two subsets. All five patients (Cases 9 to 11 and 17 and 18) who had suspicious or negative postoperative electrocardiograms but abnormally high CK-MB values had other evidence of myocardial necrosis in additional tests, whereas additional evidence for perioperative myocardial infarction was lacking in those five patients (Cases 12 to 16) with electrocardiographic changes suggesting infarction but normal CK-MB values.

Technetium-99m scintigraphy: This test confirmed the presence of perioperative myocardial infarction in six of seven tested patients with new Q waves (Cases 1 to 6) but was negative in one patient with an inferior myocardial infarction (Case 7). It further supported positive enzyme criteria for perioperative myocardial infarction in two patients with a suspicious or negative postoperative electrocardiogram (Cases 11 and 17) and was negative in one patient (Case 18) with enzyme values indicative of perioperative myocardial infarction. The preoperative image of this patient showed grade 3 focal uptake which decreased to grade 1 in the postoperative image. Preoperative images were positive in an additional four patients including Patient 5 with a perioperative myocardial infarction; after operation two of these scintigrams decreased to a grade 1 or 2 diffuse pattern, one scan was stable and one scan showed a definite increase in localized activity (Case 5) indicative of perioperative myocardial infarction. A grade 2 diffuse pattern was observed preoperatively in five patients. After operation the scintigram remained unchanged in four patients and uptake of isotope decreased in one patient. None of these five patients had perioperative infarction. No new diffuse patterns were observed after operation.

Discussion

CK-MB in diagnosis of perioperative myocardial infarction: Results of this study suggest that serum CK-MB analysis by column chromatography is more sensitive than the electrocardiogram or technetium-99m scintigram in detecting the occurrence of a perioperative myocardial infarction. This sensitive method permitted the definition of a "normal" or expected range of perioperative CK-MB release in a control group of patients at minimal risk for the development of myocardial necrosis. This increase in serum CK-MB activity in the control group may be attributed to surgical trauma such as the insertion of a sump drain or ligation of the right atrial appendage. In this study myocardial tissue damage associated with coronary arterial bypass surgery was usually very small, and perioperative CK-MB enzyme levels were generally lower than those found after closure of an atrial septal defect in a person with normal coronary arteries. Thus, in the absence of concomitant surgical procedures, for example an aneurysmectomy, an increase in perioperative serum CK-MB activity to levels greater than those of the control group was most likely the result of myocardial necrosis and reperfusion during surgery. This concept was supported by either electrocardiographic and scintigraphic abnormalities or serum enzyme (LDH and SGOT) elevations in all patients with serum CK-MB activity greater than the control values, and it allowed us to separate patients into groups with and without a perioperative myocardial infarction.

Although our upper limits of expected perioperative CK-MB activity and limits for the concentration-time integral were well supported by the results of this study, it is clear that a continuous spectrum of perioperative CK-MB activity occurs after coronary bypass surgery. In some instances it may be difficult to define where nonspecific surgical trauma ends and ischemic injury begins. Therefore, it is necessary not only to use a sensitive method of CK-MB analysis, but also to define a range of expected perioperative CK-MB serum enzyme activity for each institution. CK-MB analysis provides

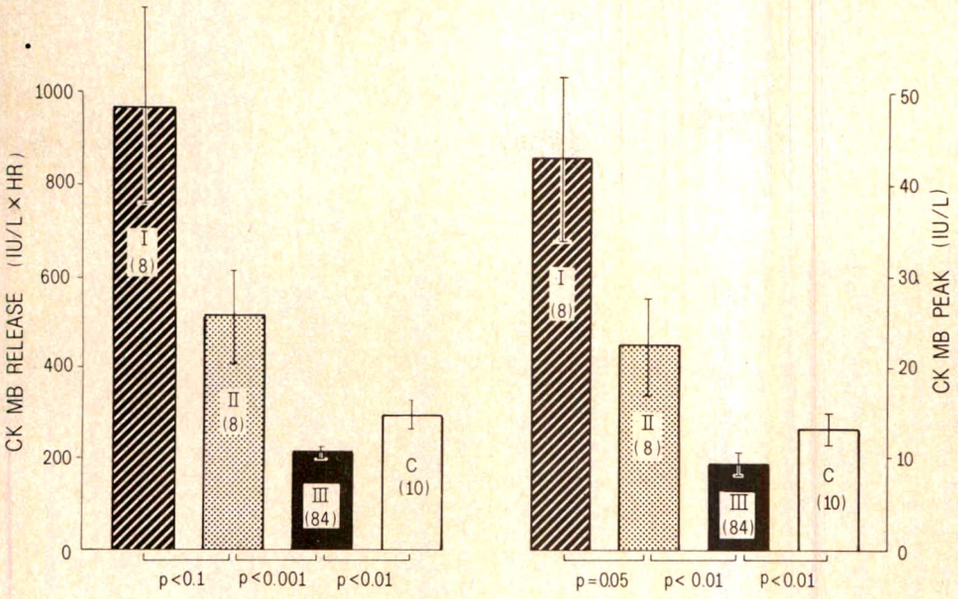

FIGURE 2. Mean postoperative CK-MB release and CK-MB peak values for all groups (± standard error). Roman numerals I, II and III designate the three groups; Arabic numbers indicate the number of patients in each group. C = control group; HR = heart rate; other abbreviations as in Figure 1.

TABLE II

Detection of Perioperative Myocardial Infarction

Case no.	ECG†	Scan‡	CK-MB Peak (>23 IU/liter)§	CK-MB Integral (>488 IU/liter × hr)§	SGOT Peak (>90 IU/liter)§	LDH Isoenzymes (>220 IU/liter§	$LDH_1 \geq LDH_2$)
			Electrocardiographic Group I				
1*	+	+	31	684	102	414	+
2*	+	+	93	2348	499	1524	+
3*	+	+	36	870	138	533	+
4*	+	+	33	641	101	472	+
5*	+	+	68	1304	98	492	+
6*	+	+	26	715	91	400	+
7*	+	−	29	514	119	401	−
8*	+	0	27	689	199	636	+
			Electrocardiographic Group II				
9*	(+)	0	31	765	132	476	+
10*	(+)	0	24	562	65	458	+
11*	(+)	+	55	1114	144	590	+
12	(+)	0	12	316	61	392	−
13	(+)	0	14	347	81	314	−
14	(+)	0	13	314	58	317	−
15	(+)	0	15	307	69	285	−
16	(+)	−	13	382	61	291	−
			Electrocardiographic Group III				
17*	−	+	25	687	82	273	+
18*	−	−	31	593	94	410	+
19–21	−	−	−	−	128, 129, 166	−	−
22–23	−	−	−	−	−	261, 304	+
17–100 mean ± SD (range)	−	− (0 in 24 pts)	8.8 ± 3.2 (3–18)	198 ± 63 (70–395)	41 ± 13 (20–78)	238 ± 49 (130–403)	−
			Control Group				
1–10 mean ± SD (range)	−	0	13.1 ± 5.1 (6–20)	294 ± 97 (136–438)	46 ± 11 (26–62)	267 ± 39 (220–346)	−

* Patients with perioperative myocardial infarction.

† + = electrocardiogram indicative of perioperative myocardial infarction (electrocardiographic group I); (+) = electrocardiogram suggestive of perioperative myocardial infarction (group II).

‡ + = scans that became positive in the postoperative period.

§ Values in parentheses indicate upper limits used as criteria for perioperative myocardial infarction in this study.

0 = not done; − = negative for perioperative infarction.

pts = patients; SD = standard deviation.

TABLE I

Clinical Data on Control Patients

Case no.	Age (yr) & Sex	Surgical Procedure	Pump Time (min)	Hypothermia (C°)	Aortic Cross-Clamp Time (min)	CK-MB Release (IU/liter × hr)	Peak CK-MB (IU/liter × hr)
1	44F	ASD II closure	56	27	. . .	413	20
2	17F	ASD II closure	26	. . .	. . .	438	20
3	66F	ASD II closure	70	30	. . .	269	11
4	40F	ASD II closure	22	. . .	9	283	10
5	20M	ASD II closure	18	. . .	. . .	389	18
6	63F	ASD II closure	17	. . .	. . .	136	6
7	46M	ASD II closure	30	. . .	. . .	216	9
8	52F	ASD SV closure	65	30	. . .	265	16
9	42F	Open valvotomy for mitral stenosis	16	35	. . .	207	8
10	26F	Closed valvotomy for mitral stenosis	. . .	. . .	. . .	321	13
Mean ± SD	42 ±17		36 ±22			294 ±97	13.1 ±5.1

ASD II = atrial septal defect, secundum type; SD = standard deviation. SV = sinus venosus type; . . . = not utilized.

the remaining 84 patients nonspecific ST-T changes were present in the initial postoperative electrocardiogram (group III). No patient had development of new bundle branch block or atrioventricular block. Postoperative electrocardiograms of all control patients remained unchanged or contained nonspecific ST-T changes. Pertinent clinical data on this group are listed in Table I.

Serum CK-MB activity: All patients had CK-MB values of less than 2 IU/liter before operation. Time-activity curves, peak CK-MB levels and the time-integrated values of all groups are depicted in Figures 1 and 2. An increase in serum enzyme activity was observed in each patient, but the pattern of enzyme release differed significantly among groups. Patients with nonspecific electrocardiographic changes (group III) exhibited only a small transient increase in mean CK-MB activity with an early peak of less than 10 IU/liter, and serum enzyme activity returned to normal within 24 hours after operation. Mean values of peak CK-MB were less than those of the control group. CK-MB exceeded 20 IU/liter in every patient with electrocardiographic evidence of new transmural infarction (group I) and enzyme activity peaked later and was elevated for a longer period of time. Mean enzyme values in group II (electrocardiographic changes suggesting infarction) were significantly higher than those in group III, but the mean value exceeded 20 IU/liter by 1 IU/

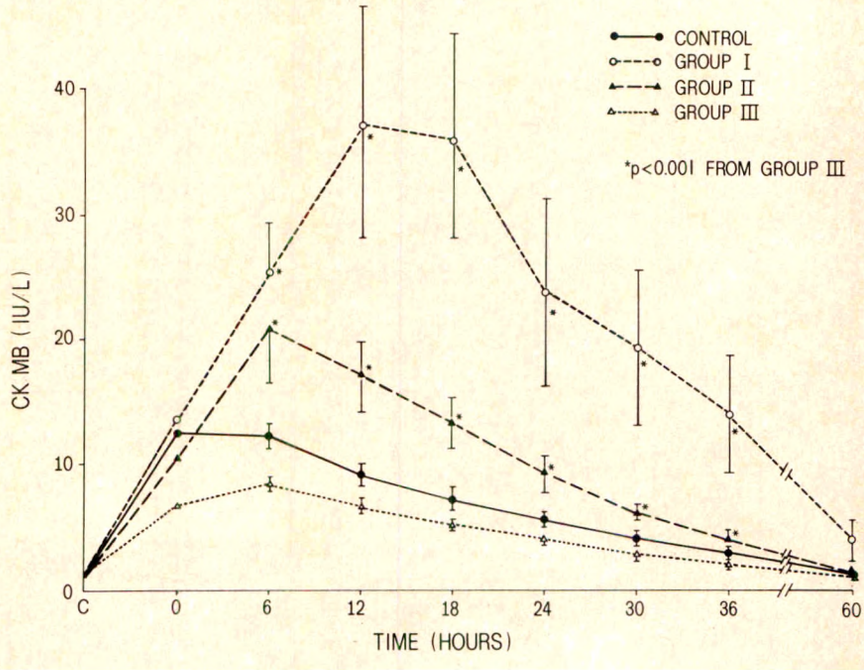

FIGURE 1. Mean CK-MB values for all groups (± standard error). Differences between groups I and II are significant at 12, 30 and 36 hours ($P < 0.05$) and at 18 hours ($P < 0.01$). C = preoperative control value; L = liter; p = probability; 0 = immediately after operation.

transmural myocardial infarction. However, CK-MB analysis by electrophoresis has also failed to separate reliably patients with and without perioperative injury.[14,17–20,22] Analysis of CK-MB levels by ion exchange column chromatography appears to be a more sensitive, precise and accurate method of measuring this isoenzyme. This method is capable of measuring CK-MB in some normal persons.[32–34]

The purpose of the present study was to determine the extent of release of CK-MB after coronary arterial bypass graft surgery and to define the usefulness of this isoenzyme for detection of perioperative myocardial infarction in comparison with standard enzyme testing, electrocardiography and technetium-99m scintigraphy in a prospective study of consecutive patients.

Methods

Patients: One hundred two consecutive patients undergoing coronary bypass graft surgery between February and August 1977 served as subjects of this study. Excluded were patients who had associated valve replacement and plication or resection of a ventricular aneurysm. Two patients did not survive operation, leaving 100 patients for inclusion in this study. The mean age (± standard deviation) of these 91 men and 9 women was 58 ± 8 years (range 38 to 79). The preoperative electrocardiograms were interpreted as indicating an old myocardial infarction in 34 patients. Ten patients with normal coronary arteries who underwent closure of an atrial septal defect (eight patients) or mitral valvotomy for isolated mitral stenosis (two patients) were evaluated with the same protocol and served as controls. This group was selected to assess the amount of CK-MB release after cardiopulmonary bypass in the absence of left ventricular hypertrophy or coronary artery disease.

Surgical technique: Bypass grafts were fashioned to one coronary artery in 12 patients, to two coronary arteries in 48 patients and to three coronary arteries in 40 patients. Operative techniques included extracorporeal circulation at an average flow rate of 2.2 liters/min per m^2, systemic hypothermia of 26° to 30° C, moderate hemodilution and electric fibrillation and defibrillation of the heart when necessary. In 72 patients ventricular fibrillation and topical hypothermia were used with coronary perfusion maintained as long as feasible. In 12 patients of this group distal anastomosis was performed with short-term aortic cross clamping. In the other 60 patients the distal anastomosis was accomplished with local occlusion of the coronary artery only and without cross clamping of the aorta. In the remaining 28 patients the heart was arrested with a cold cardioplegic solution, and coronary arterial perfusion was interrupted by continuous aortic cross clamping. Left ventricular venting was performed through the left atrium or a pulmonary vein in 37 patients and through the left ventricular apex in 63 patients. Cardiopulmonary bypass time ranged between 49 and 264 minutes (mean 127 minutes).

Electrocardiography: Twelve lead electrocardiograms were obtained within 48 hours before operation, on the 1st and 3rd postoperative day, and then at least twice during the following week. They were interpreted without knowledge of the results of serum enzyme values and categorized into three groups: group I (8 patients), definite perioperative myocardial infarction (the appearance of new Q waves of 0.04 second or greater after operation); group II (8 patients), possible perioperative myocardial infarction (1 mm horizontal S-T segment depression persisting for 48 hours after operation or new Q waves of less than 0.04 second or deep persistent T wave inversions appearing in the initial hours after operation); and group III (84 patients), nonspecific ST-T changes.

Serum enzymes: Blood samples for CK-MB isoenzymes were obtained within 24 hours before operation, immediately after closure of the chest and then at 6 hour intervals for the initial 36 hours; a final sample was obtained 60 hours after operation. The samples were immediately frozen and analyzed later with ion exchange column chromatography, a method that is sufficiently sensitive to detect CK-MB in most normal patients.[33] Details of this method and its biologic variability in our laboratory have previously been described.[34] Serum glutamic oxaloacetic transaminase (SGOT) was measured from samples obtained in the first 3 days after operation with the method of Amador and Wacker.[35] Lactate dehydrogenase (LDH) isoenzymes were analyzed with the method of Elevitch et al.[36] on blood samples obtained on the 2nd day after surgery. Upper limits of normal values in our laboratory are as follows: total CK 90 IU/liter, CK-MB 2 IU/liter, SGOT 30 IU/liter, and total LDH 220 IU/liter.

The following enzyme values were considered suggestive of perioperative myocardial infarction: (1) elevation of total LDH activity with LDH_1 isoenzyme equal to or greater than LDH_2 isoenzyme; (2) SGOT activity equal to or greater than 90 IU/liter; (3) peak CK-MB and CK-MB release over the first 36 hours after surgery exceeding the mean value + 2 standard deviations of the control group (23 IU/liter and 488 IU/liter × hour, respectively). The area inscribed by the CK-MB concentration-time curve for the first 36 hours after operation was calculated using the sum of seven successive trapezoids.[17] This integral was used to estimate total CK-MB release. It represents only a clinical approximation because of the complexity of CK-MB kinetics.[37–43]

Postoperative technetium-99m myocardial scintigraphy: This procedure was performed in the last 65 consecutive patients, of whom 44 also had a preoperative scintigram. Imaging was performed within 48 hours before operation and 48 to 96 hours after operation using a Searle Pho-Gamma L.F.O.V. system with a low energy all-purpose (L.E.A.P.) parallel hole collimator. One to 2 hours after intravenous injection of 15 mCi of technetium-99m pyrophosphate, images were obtained in the anterior, 45° and 60° left anterior oblique and in the left lateral projection, counting 300,000 counts per image with a 20 percent window. Scintigrams were graded from 0 to four as previously described,[26,27] where 0 represented no uptake of technetium-99m pyrophosphate by the myocardium and grade 4 represented uptake by the myocardium to a greater extent than the sternum. In addition, uptake was graded as localized or diffuse. The scintigrams were analyzed independently by two observers and interpreted as positive for perioperative myocardial infarction when new grade 2 to 4 localized uptake was present in the postoperative image.

The unpaired t test was used for statistical analysis of differences between subsets of patients.

Results

Electrocardiograms: Diagnostic electrocardiographic changes of acute myocardial infarction were observed in eight patients (group I). The site of infarction was inferior in five patients, anterior in two and lateral in one. Saphenous vein grafts were fashioned to all arteries supplying the infarcted areas. In eight patients electrocardiographic changes suggested the presence of myocardial infarction (group II). In four of these patients (groups I and II) electrocardiographic changes first appeared on the 3rd postoperative day. In

Serum Myocardial Creatine Kinase (CK-MB) After Coronary Arterial Bypass Surgery

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Serum myocardial creatine kinase, MB isoenzyme (CK-MB) was measured at 6 hour intervals for 36 hours after surgery by ion exchange column chromatography for detection of perioperative myocardial infarction and was compared with serial electrocardiograms, serum glutamic oxaloacetic transaminase (SGOT) and lactate dehydrogenase (LDH) isoenzyme determination and technetium-99m pyrophosphate myocardial scintigraphy in 100 consecutive patients undergoing coronary artery bypass surgery. Results were compared with those in a control group of 10 patients with normal coronary arteries after closure of an atrial septal defect or mitral valvotomy. Total CK-MB release was estimated by calculating the concentration time integral for 36 hours after surgery. In 77 of 87 patients with a peak CK-MB and total CK-MB release lower than the highest control value (or mean + 2 standard deviations), all other tests were also negative for perioperative myocardial infarction. The other 10 patients had an isolated positive laboratory test (5 patients showed ischemic electrocardiographic changes, 3 patients an SGOT level of more than 90 IU/liter and 2 patients LDH_1 equal to or greater than LDH_2). All 13 patients with CK-MB values higher than the highest control value (or mean ± 2 standard deviations) had at least two additional positive laboratory tests indicating perioperative myocardial infarction (8 patients had new Q waves, 3 patients ischemic electrocardiographic changes, 11 patients LDH_1 equal to or greater than LDH_2, 11 patients SGOT greater than 90 IU/liter and 8 of 10 patients a positive myocardial scintigram). Thus, CK-MB by column chromatography is a reliable test for recognition of perioperative myocardial infarction and appears to be more sensitive than electrocardiography or scintigraphy for detection of myocardial necrosis. Reliability may be strengthened by the association of elevated CK-MB with additional positive tests.

Although surgical myocardial revascularization has become a widely accepted form of treatment for relief of angina pectoris,[1,2] and although the operative mortality is less than 2 percent in some series,[3–5] there remains a risk of loss of myocardium due to perioperative myocardial infarction.[3–18] Differing criteria for the recognition of perioperative myocardial infarction have resulted in a reported incidence varying between 2 and 30 percent.[3–18] This event contributes substantially to morbidity and mortality in the postoperative period.[7,16]

Recently technetium-99m pyrophosphate myocardial scintigraphy and measurement of blood myocardial creatine kinase (CK-MB) by electrophoresis and fluorometric scanning have been added to our diagnostic procedures.[9,10,14,17–22] However, neither technique alone is capable of clearly identifying those patients with perioperative myocardial infarction. The difficulties in interpretation of some diffuse patterns of pyrophosphate myocardial scintigraphy have led several investigators[23–31] to question its sensitivity and specificity for detection of non-

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who had mitral valve replacement. Two dimensional echocardiography can differentiate ruptured chordae tendineae from mitral valve prolapse and can detect ruptured chordae in the presence of rheumatic disease. Identification of ruptured chordae tendineae implies significant mitral insufficiency and usually leads to surgical therapy.

Papillary muscle dysfunction: Isolated injury of one papillary muscle will not cause mitral insufficiency; rather, injury to both papillary muscles or injury that also involves the left ventricular wall[18] is required. Distortion of the normal spatial relations of the papillary muscles results in a loss of the normal structural support of the mitral valve.[19] In one series[12] papillary muscle dysfunction was responsible for 11 percent of cases of mitral insufficiency. The most common cause of papillary muscle dysfunction is coronary artery disease. Papillary muscles are sensitive to ischemia because of a precarious blood supply and a relatively increased oxygen demand. Other causes of papillary muscle dysfunction include any cardiomyopathy, any cause of left ventricular dilatation, trauma, endocardial diseases, infiltrative diseases or inflammatory diseases.

Nineteen of our 140 patients with mitral insufficiency had papillary muscle dysfunction. Two dimensional echocardiography showed diffuse or segmental wall motion abnormalities involving the base of one or both papillary muscles and the adjacent left ventricular wall. It was not always possible to distinguish the papillary muscle dysfunction of coronary artery disease from that of a more diffuse myopathic process, nor was it possible to differentiate left ventricular dysfunction with mitral insufficiency from that without mitral insufficiency. However, mitral insufficiency secondary to left ventricular dysfunction could be differentiated from mitral insufficiency due to valve disease.

Mitral anular calcification: This condition, usually regarded as a degenerative disorder, frequently occurs in the aged population. Rheumatic heart disease, hypercalcemic disorders, hemodialysis and accelerated atherosclerosis may be associated with premature anular calcification.[20] The calcific process may invade the septum to cause conduction disturbances, but it rarely extends to involve the leaflets.[20] Anular calcification presumably causes mitral insufficiency by preventing the normal systolic conformational change in the anulus or by interfering with leaflet motion; mitral insufficiency is rarely significant, but on occasion may be severe. In our series of 140 patients, a calcified anulus was seen in 11 patients. It was readily recognized as a crescent-shaped band of echoes behind the posterior mitral leaflet.

Other causes of mitral insufficiency: *A cleft anterior mitral leaflet,* the most common form of congenital mitral insufficiency, occurred in five patients. A cleft mitral leaflet, usually in association with an ostium primum atrial septal defect, is a form of partial endocardial cushion defect. Two dimensional echocardiography can recognize a cleft anterior mitral leaflet and can identify the specific types of endocardial cushion defect.[21,22]

Five patients had idiopathic hypertrophic subaortic stenosis. The mechanism of mitral insufficiency in this disease is controversial; the abnormal left ventricular shape, the misaligned anterior papillary muscle and the systolic anterior motion of the mitral valve have all been implicated.

A left atrial myxoma, important in the differential diagnosis of mitral stenosis, can also cause mitral insufficiency. Repeated prolapse of the tumor through the mitral valve orifice can traumatize the mitral valve and produce mitral insufficiency; this was the mechanism of the insufficiency in our patient.

Unknown cause: We were unable to identify a cause of mitral insufficiency in seven patients. Invasive study in four of the seven patients was similarly nondiagnostic. Because none of these patients required valve replacement, the anatomic diagnosis remains a mystery. These patients may have had one of the common causes of mitral insufficiency that was not detected with two dimensional echocardiographic study. Nevertheless, such study can determine the cause of mitral insufficiency with the same sensitivity as cardiac catheterization.

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symptoms of various degrees of severity. Although, these patients are not representative of all patients with mitral insufficiency, they are an adequate referral group for testing the ability of two dimensional echocardiography to separate causes of mitral insufficiency and provide therapeutic and prognostic information.

Mitral valve prolapse: In our series, mitral valve prolapse was the most common cause of clinical mitral insufficiency. Two mechanisms for the abnormal mitral valve motion have been proposed.[11] First, the valvular heart disease includes myxomatous leaflet degeneration, chordal elongation, redundant leaflet tissue or rheumatic endocarditis. Variance between left ventricular and mitral anular size and between mitral leaflet and chordal size may cause prolapse of the leaflet into the left atrium. Second, asymmetric patterns of myocardial contraction involving the papillary muscles may cause the prolapse.

Mitral valve prolapse is a common entity. Clinical diagnosis depends on auscultation of a mid systolic click or late systolic murmur, or both. In our series of 140 patients with clinical mitral insufficiency, 41 patients had mitral prolapse but only half of the latter group had a click or a late systolic murmur. Thus, two dimensional echocardiography appears to be sensitive in detecting valve prolapse; patients thought to have mitral insufficiency from another cause may often have prolapse.

The characteristic two dimensional echocardiographic criteria for the diagnosis of mitral valve prolapse have been defined.[3] These criteria include arching of the leaflets above the mitral anulus into the left atrium; the point of leaflet coaptation is preserved. This results in accentuation of the angle between the anterior leaflet and the posterior aortic wall (in anterior leaflet prolapse) or of the angle between the posterior leaflet and the left atrial posterior wall (in posterior leaflet prolapse). Vigorous systolic mitral anular motion is also seen. Most of our patients (31 of 41) had prolapse of both leaflets, 9 had isolated posterior leaflet prolapse and 1 had isolated anterior leaflet prolapse. The presence of mitral prolapse and mitral insufficiency was confirmed in each of the 13 patients who had diagnostic cardiac catheterization.

Mitral valve prolapse only occasionally causes severe mitral insufficiency. Thus, although it may be the most common cause of clinical mitral insufficiency, it is an unusual cause of hemodynamically significant mitral insufficiency. The severity of the mitral insufficiency in patients with mitral prolapse cannot be predicted with two dimensional echocardiography. Four of our patients had significant mitral insufficiency at catheterization. Because many of the patients were hospitalized for invasive studies, this 10 percent incidence rate of severe mitral insufficiency in mitral prolapse is probably not seen in an outpatient group.

Rheumatic mitral insufficiency: In most series of clinical and hemodynamically significant mitral insufficiency, a rheumatic cause predominates.[12] However, pure rheumatic mitral insufficiency is less common than pure mitral stenosis or a combined lesion. Pathologic study in cases of pure mitral insufficiency shows a loss of leaflet tissue from fibrosis and contraction with thickened, fused chordae tendineae.[13] Commissural fusion is unusual in pure insufficiency,[13] but typical of combined lesions. Fibrosis and fusion of the posterior leaflet with little abnormality of the anterior leaflet can occur.[14] In our series of 140 patients with clinical mitral insufficiency, a rheumatic cause was second in frequency. Characteristic two dimensional echocardiographic findings are limited to the mitral leaflets. In diastole the motion of the anterior leaflet results in a right angle bend of the leaflet; the motion of the posterior leaflet is greatly restricted.

In patients with significant clinical rheumatic mitral insufficiency, those with pure insufficiency may be separated from others with combined mitral stenosis and insufficiency. In patients with pure insufficiency anterior leaflet motion is only mildly restricted, and diastolic mitral orifice size is normal or minimally reduced; in combined lesions anterior leaflet motion is more restricted and the size of the diastolic mitral valve orifice is significantly reduced. Ten of 37 patients with rheumatic disease had pure mitral insufficiency. In each of these 10 patients, measurement of the two dimensional echocardiographic mitral valve orifice was normal; and each of the 8 patients who underwent cardiac catheterization had significant mitral insufficiency without stenosis. By contrast, 27 patients had a combined lesion. In each of these patients, measurement of the two dimensional echocardiographic mitral valve orifice was less than 2.0 cm^2; and each of the 13 patients who underwent cardiac catheterization had significant mitral stenosis, but only modest mitral insufficiency. The two dimensional mitral valve area was similar to the catheterization mitral valve area after allowances for the mild amounts of mitral insufficiency present. Thus, patients with rheumatic mitral insufficiency may be separated into two groups: those with pure insufficiency in whom the amount of insufficiency may be severe and those with combined lesions in whom the amount of insufficiency is typically modest.

Ruptured chordae tendineae: This is the most common cause of acute mitral insufficiency. Pathologically, most patients with ruptured chordae tendineae have no underlying heart disease,[15,16] but ruptured chordae can also occur secondary to rheumatic disease, endocarditis, mitral prolapse, Ehlers-Danlos syndrome, idiopathic hypertrophic subaortic stenosis, trauma and myocardial infarction.[15–17] Patients with spontaneous chordal rupture more often have posterior leaflet involvement; patients with secondary chordal rupture have equal involvement of the anterior and posterior leaflets.[17]

Fourteen of our 140 patients had ruptured chordae tendineae; rupture was primary in 11 patients (involving the posterior leaflet in 7 and the anterior leaflet in 4) and was secondary to endocarditis in 2 patients and to rheumatic disease in 1 patient (all 3 with anterior leaflet involvement). Other causes of ruptured chordae were not seen. Each of the 11 patients who underwent cardiac catheterization had significant mitral insufficiency. The diagnosis was confirmed at operation in the 11 patients

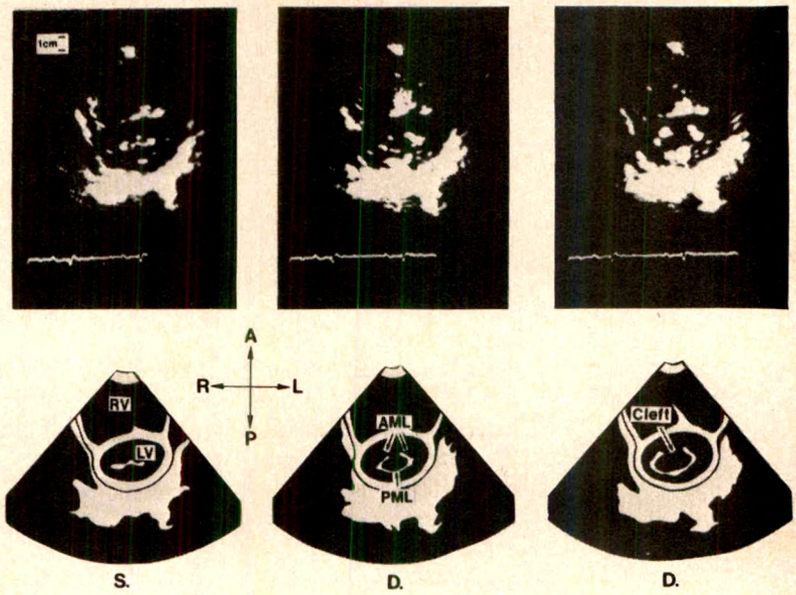


FIGURE 7. Two dimensional echocardiogram (transverse view) from a patient with mitral insufficiency secondary to a cleft anterior mitral leaflet. Systolic (S.), early diastolic (D.) and late diastolic frames appear from left to right. During systole the mitral valve appears as a linear structure within the left ventricle (LV). During diastole the anterior leaflet (AML) opens into two components as would a drawbridge. A distinct cleft is apparent. Posterior leaflet (PML) motion is normal. Unidentified abbreviations as in Figures 1 and 2.

associated atrial septal defect, and one had an associated aortic coarctation. Three patients had surgery; each had a cleft anterior mitral leaflet that was repaired.

Idiopathic hypertrophic subaortic stenosis (five patients): On two dimensional study each of these patients had asymmetric septal hypertrophy and systolic anterior motion of the mitral valve. Four patients had cardiac catheterization. All patients had a left ventricular outflow tract gradient at rest or on provocation. Mitral insufficiency was present in all five patients but was significant (3+) in only one patient. No patient had surgery.

Atrial myxoma (one patient): The two-dimensional study in this patient showed a large echo-dense mass moving from the left atrium into the left ventricular inflow tract during late diastole (Fig. 8). At cardiac catheterization, significant (3+) mitral insufficiency was present. The tumor was excised and the mitral valve replaced.

Unknown (seven patients): These patients had no identifiable cause of mitral insufficiency. Two dimensional echocardiographic studies revealed normal mitral valve leaflets, a normal mitral anulus and normal left ventricular wall motion. Four patients had cardiac catheterization. All patients had mitral insufficiency (from 1 + to 3+ in severity) and normal left ventricular wall motion. One patient had significant coronary artery disease. Catheterization study did not define the cause of mitral insufficiency in these patients.

Discussion

Previous studies have evaluated the causes of mitral insufficiency and their prevalence. These studies utilized invasive diagnostic and surgical data or data obtained at autopsy. However, not all patients require cardiac catheterization. In patients with severe angiographic mitral insufficiency, it may be difficult to define the cause. Ideally, two dimensional echocardiography should be used to separate patients who can be treated surgically from those who cannot be so treated and those with potentially progressive disease from those with benign disease. We studied 140 consecutive patients with a murmur of mitral insufficiency.[10] The patients studied included inpatients and outpatients who had

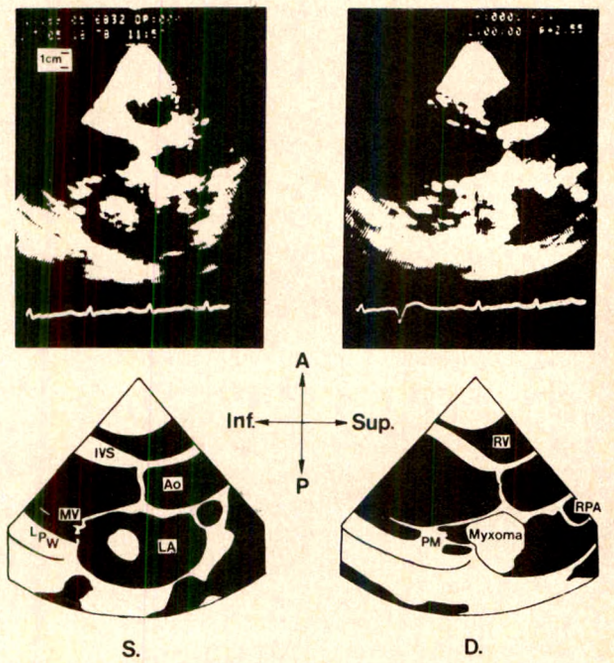


FIGURE 8. Two dimensional echocardiogram from a patient with a left atrial myxoma. Systolic (S.) and diastolic (D.) frames of the long axis view are shown. During systole the myxoma appears as a dense mass of echoes within the left atrium (LA). During diastole the myxoma prolapses across the mitral valve (MV) into the left ventricular inflow tract. PM = papillary muscle; RPA = right pulmonary artery; other abbreviations as in Figure 1.

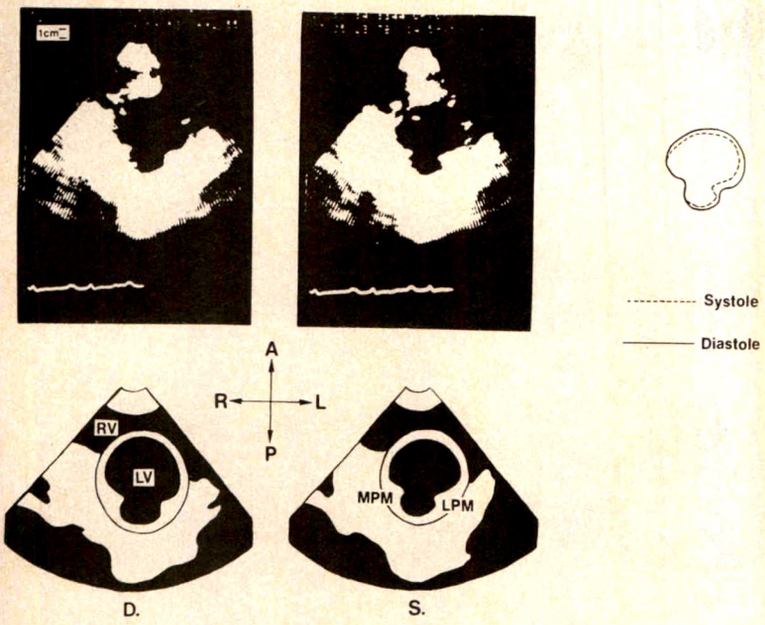


FIGURE 5. Two dimensional echocardiogram (transverse view at the level of the papillary muscle) from a patient with mitral insufficiency secondary to papillary muscle dysfunction. End-diastolic (D.) and end-systolic (S.) frames are accompanied by a line drawing of superimposed diastolic (**solid line**) and systolic (**dotted line**) endocardial surfaces. The medial papillary muscle (MPM) is akinetic, the lateral papillary muscle (LPM) is hypokinetic and left ventricular (LV) wall motion is also hypokinetic. Unidentified abbreviations as in Figures 1 and 2.

muscles. Papillary muscle motion was best assessed in the transverse views (Fig. 5). The mitral valve leaflets and the mitral anulus were anatomically normal.

Eight patients had cardiac catheterization; all had diffuse or segmental angiographic abnormalities of left ventricular wall motion. The severity of mitral insufficiency varied from 1+ to 4+. Seven patients had coronary artery disease and one had cardiomyopathy. None was a surgical candidate.

Mitral anular calcification (11 patients): One of these patients also had rheumatic mitral valve disease; two also had idiopathic hypertrophic subaortic stenosis and one also had left ventricular dysfunction. The calcified anulus appeared as a dense, crescent-shaped band of echoes between the posterior mitral leaflet and the left ventricular posterior wall (Fig. 6).

Three patients underwent diagnostic cardiac catheterization. One had significant (3+) mitral insufficiency; two had mild (1+) mitral insufficiency. None had surgery.

Cleft anterior mitral valve leaflet (five patients): On two dimensional study, systolic mitral valve motion in these patients was normal; however, during diastole the anterior leaflet of the mitral valve opened, like a drawbridge, into two distinct components (Fig. 7). Posterior leaflet motion was normal.

Four patients were studied with cardiac catheterization, and all had mitral insufficiency. Two had an

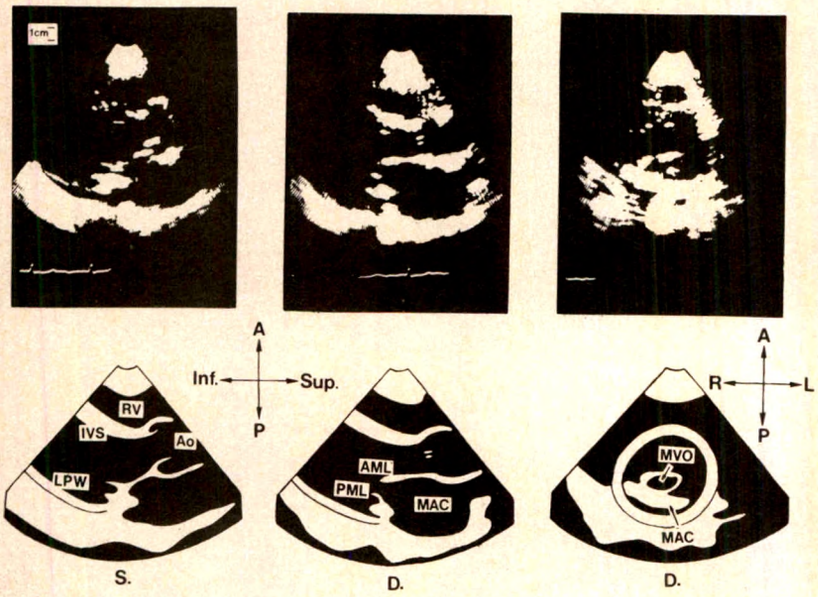


FIGURE 6. Two dimensional echocardiogram from a patient with mitral anular calcification secondary to rheumatic heart disease. The first two images show systolic (S.) and diastolic (D.) frames of the long axis view. The calcified mitral anulus (MAC) appears as an echo-dense structure at the juncture of the posterior mitral leaflet (PML) and left ventricular posterior wall (LPW). The third image shows a diastolic frame of the transverse view of the left ventricle at the level of the mitral valve. The calcified mitral anulus appears as an echo-dense crescent between the posterior mitral leaflet and the left ventricular posterior wall. Unidentified abbreviations as in Figures 1 and 2.

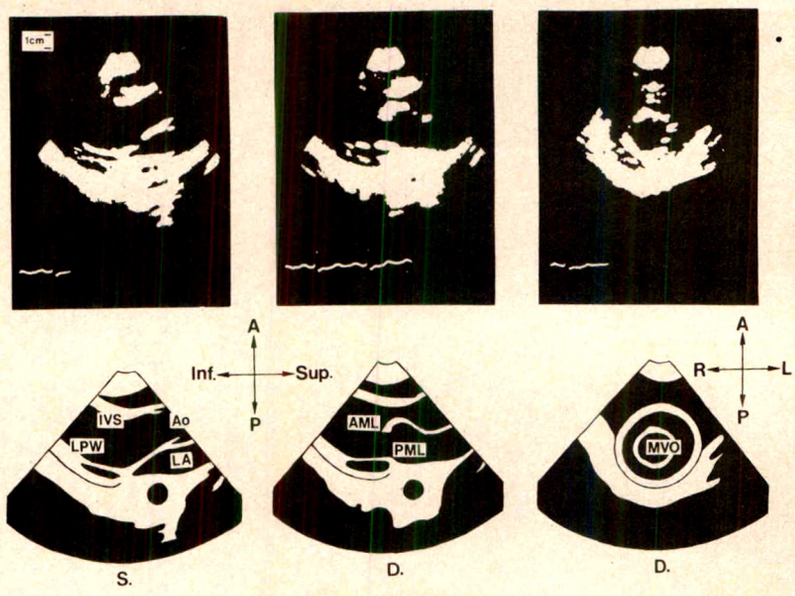
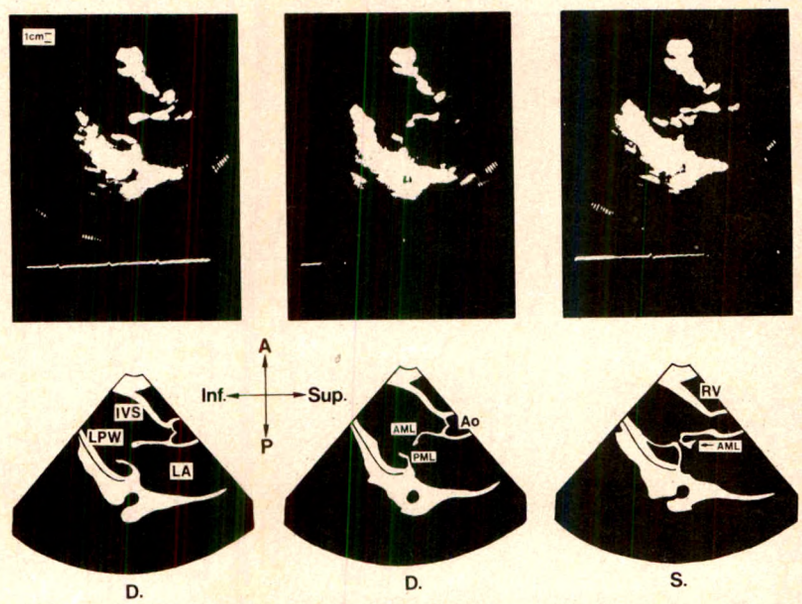


FIGURE 3. Two dimensional echocardiogram from a patient with pure rheumatic mitral insufficiency. The first two images show systolic (S.) and diastolic (D.) frames in the long axis view. Diastolic motion of the anterior mitral leaflet (AML) shows the right-angle bend of the tip of the leaflet that is typical of rheumatic mitral valve disease; however, motion of the posterior mitral leaflet (PML) is reduced. The third image shows a diastolic frame of the transverse view of the mitral valve orifice (MVO). The mitral valve area (5.5 cm^2) is normal. Unidentified abbreviations as in Figures 1 and 2.



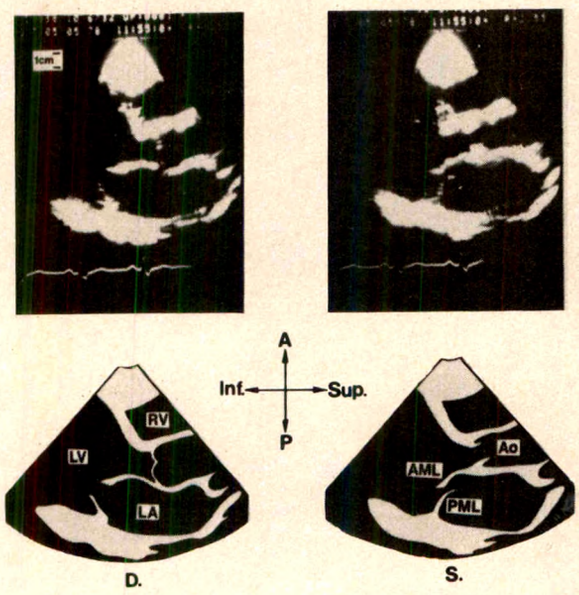


FIGURE 4. Two dimensional echocardiograms (long axis views) from two patients with ruptured chordae tendineae. **Top,** mid and end-diastolic (D.) and systolic (S.) frames from a patient with flail anterior mitral leaflet (AML). The tip of the anterior mitral leaflet moves past the posterior mitral leaflet (PML) into the left atrium (LA). Maximal abnormal leaflet motion occurs at the tip of the leaflet; normal coaptation between the leaflets is lost. **Bottom,** mid diastolic and systolic frames from a patient with a flail posterior mitral leaflet. Similarly, the tip of this leaflet moves past the anterior mitral leaflet into the left atrium. Maximal abnormal leaflet motion occurs at the tip; normal coaptation is lost. Unidentified abbreviations as in Figure 1.

Mitral valve prolapse (41 patients): Fourteen patients had a mid systolic click with a late systolic murmur, 5 had only an apical late systolic murmur and 22 only an apical holosystolic murmur.

Two dimensional echocardiographic studies revealed prolapse of the anterior and posterior mitral leaflets in 31 patients, of the posterior leaflet only in 9 patients and of the anterior leaflet only in 1 patient. Characteristic findings were best seen in the longitudinal view. The abnormal leaflet arched superiorly above the mitral anular ring into the left atrium; the abnormal leaflet motion was localized to the body of the leaflets, and the coaptation point at the tips of the leaflets remained intact (Fig. 1). Other characteristic findings included vigorous inferior systolic anular motion and anterior displacement of the coaptation point (indicating a relatively larger posterior leaflet). Mitral valve prolapse was also assessed from the apical view.

Thirteen patients underwent diagnostic cardiac catheterization. All had mitral valve prolapse with mitral insufficiency; four had at least 3+ mitral insufficiency. The severity of mitral insufficiency did not correlate with leaflet involvement (anterior versus posterior versus both) or extent of leaflet prolapse.

Four patients had mitral valve replacement for severe mitral insufficiency. Surgical and pathologic findings included redundant leaflets with myxomatous degeneration and intact chordae tendineae.

Rheumatic mitral valve disease (37 patients): *Twenty-seven patients had combined mitral stenosis and mitral insufficiency.* In these patients both mitral leaflets were thickened. In the long axis view, the anterior mitral leaflet motion was reduced and the leaflet bent at a right angle during diastole; diastolic posterior leaflet motion was markedly restricted. The diastolic mitral valve orifice measured less than 2.0 cm^2 in each patient (Fig. 2). No patient with combined lesions had associated mitral valve prolapse. Thirteen patients underwent diagnostic cardiac catherterization. All had only 1+ or 2+ angiographic mitral insufficiency. The mitral valve area was significantly reduced (less than 1.8 cm^2) in each patient. Eight patients were surgically treated; six had mitral valve replacement and two had a commissurotomy.

Ten patients had pure mitral insufficiency. In these patients, both mitral leaflets were thickened. Although the anterior leaflet was bent at a right angle during diastole, motion of the mid portion of the leaflet was not reduced. Diastolic posterior leaflet motion was restricted. The diastolic mitral valve area measured at least 3.0 cm^2 in each patient (Fig. 3). Three patients also had anterior mitral leaflet prolapse; one patient also had ruptured chordae tendineae (without endocarditis). Eight patients underwent diagnostic cardiac catheterization; all had at least 3+ angiographic mitral insufficiency, and none had an end-diastolic mitral valve gradient. Six patients had mitral valve replacement for severe mitral insufficiency. Surgical findings confirmed the presence of rheumatic disease in all.

Ruptured chordae tendineae (14 patients): Two patients had endocarditis, 1 patient had known rheumatic heart disease and 11 patients had no known previous heart disease. In the long axis view there was systolic motion of the tip of the anterior (7 patients) or posterior (7 patients) mitral leaflet into the left atrium (Fig. 4). Normal coaptation of the leaflets was not present.

Eleven patients underwent diagnostic cardiac catheterization. All had 3+ or 4+ angiographic mitral insufficiency. Eleven patients had a mitral valve replacement, and surgical findings confirmed ruptured chordae tendineae in all patients.

Left ventricular dysfunction (19 patients): In these patients, two dimensional echocardiograms revealed diffuse or segmental abnormalities in left ventricular wall motion involving one or both papillary

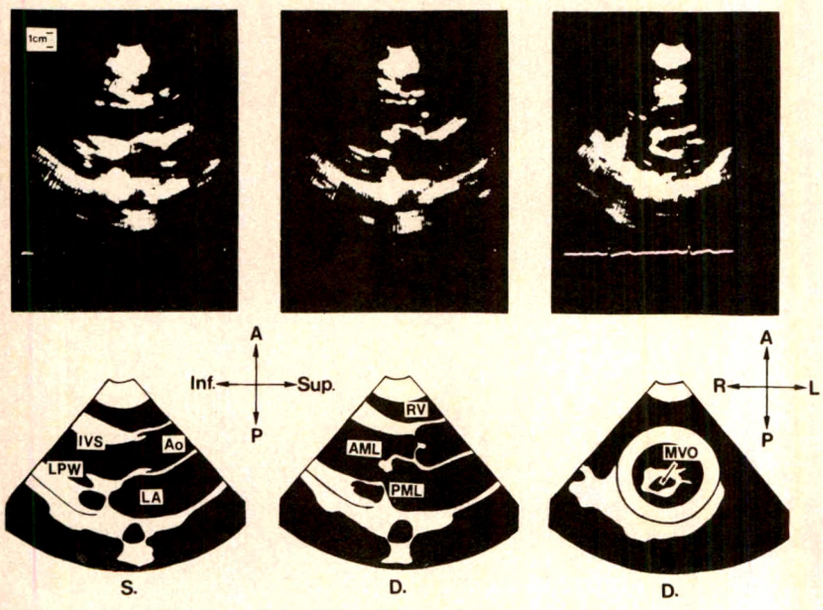


FIGURE 2. Two dimensional echocardiogram from a patient with combined mitral stenosis and insufficiency. The first two images show systolic (S.) and diastolic (D.) frames in the long axis view. Note the diastolic restriction and right-angular shape of the anterior mitral leaflet (AML) and the reduced motion of the posterior mitral leaflet (PML). Both leaflets are abnormally thick. The third image shows a diastolic frame of the transverse view of the mitral valve orifice (MVO). The mitral valve area (1.6 cm^2) is mildly to moderately reduced. L = left; R = right; other abbreviations as in Figure 1.

tographs of single frame video tape images. Such images suffer from (1) loss of visual integration that normally accompanies real time imaging, and (2) a degradation of image quality caused by photographing a single field of a complete video tape frame that normally consists of two interlaced fields. Complete analysis of mitral valve apparatus and function was accomplished with use of the long axis, tranverse and apical views. Specifically, systolic and diastolic mitral leaflet motion was evaluated using the long axis and transverse views.

Valve motion was carefully assessed to determine the presence of mitral valve prolapse according to the criteria of Gilbert et al.[3] The size of the diastolic mitral valve orifice was evaluated using the transverse view at the level of both anterior and posterior mitral leaflets according to the methods of Henry et al.[4] and Nicol et al.[5] Ruptured chordae tendineae were recognized using the criteria of Mintz et al.[6] Left ventricular wall motion was studied with the method of Kisslo et al.[7] in the long axis, transverse and apical views. The mitral anulus was evaluated in both the long axis and transverse views.

Cardiac catheterization. Diagnostic cardiac catheterization was performed in 51 patients. Cardiac output was measured using the Fick principle; and, in patients with mitral stenosis, the mitral valve area was calculated with Gorlin's formula.[8] Left ventriculography was performed in either the right anterior oblique projection or in both the right and left anterior oblique projections. The severity of mitral regurgitation was graded on a scale of 1+ (trivial regurgitation) to 4+ (full left atrial opacification on the first systole). Left ventricular wall motion was assessed by two observers.[9] Selective coronary arteriography was also performed in each patient.

Results

Sixty-one male and 79 female patients were studied. Their ages ranged from 12 to 70 years (mean 49 ± 18 years).

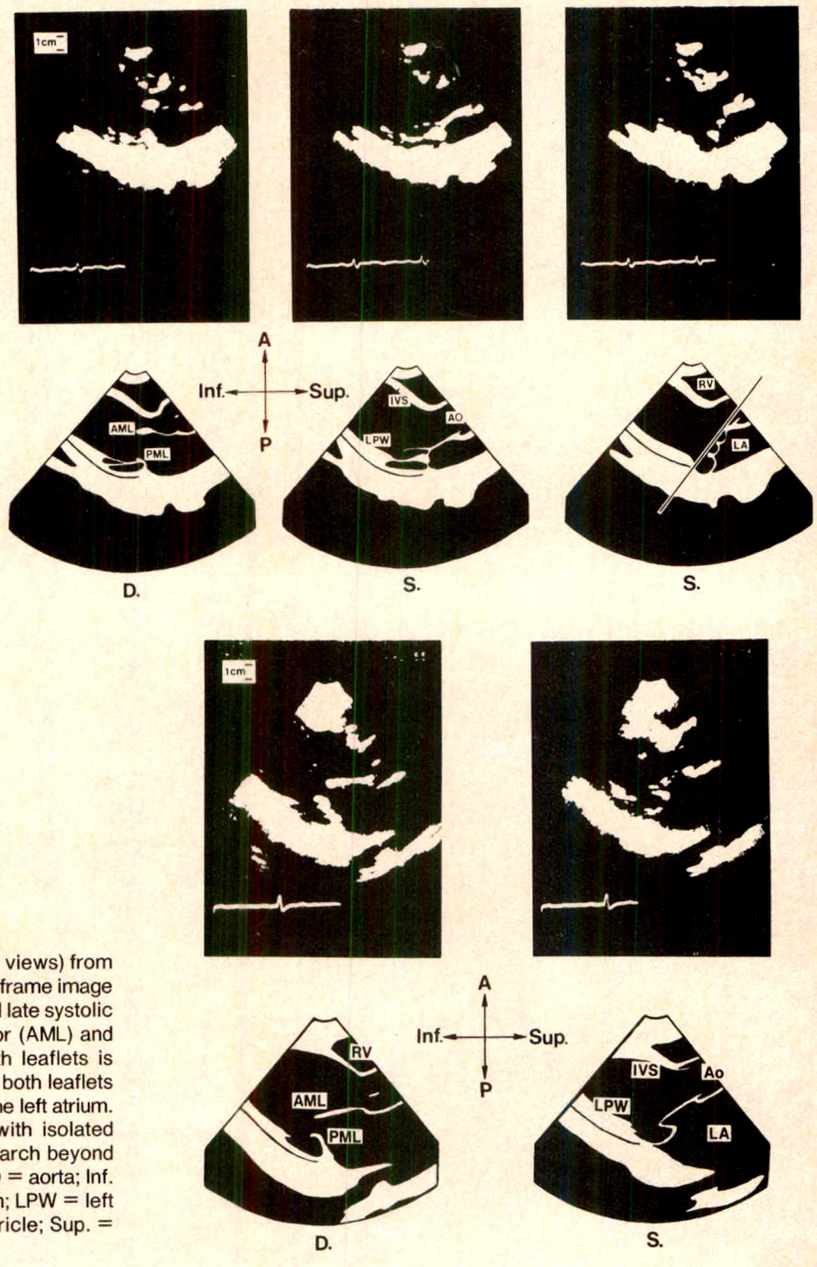


FIGURE 1. Two dimensional echocardiograms (long axis views) from two patients with mitral valve prolapse. Under each single frame image is a labeled idealized diagram. **Top,** diastolic (D.), early and late systolic (S.) frames from a patient with prolapse of both anterior (AML) and posterior (PML) mitral valve leaflets. Coaptation of both leaflets is preserved. Prolapse occurs only during late systole when both leaflets arch beyond the plane of the mitral anulus (**solid line**) into the left atrium. **Bottom,** diastolic and systolic frames from a patient with isolated posterior leaflet prolapse. The anterior leaflet does not arch beyond the plane of the mitral anulus (**solid line**). A = anterior; AO = aorta; Inf. = inferior; IVS = interventricular septum; LA = left atrium; LPW = left ventricular posterior wall; P = posterior; RV = right ventricle; Sup. = superior.

Two Dimensional Echocardiographic Evaluation of Patients With Mitral Insufficiency

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One hundred forty patients with clinical mitral insufficiency were studied with two dimensional echocardiography. Cardiac catheterization was performed in 51 patients; all had mitral insufficiency. Thirty-three patients were surgically treated. An etiologic diagnosis was made in 133 patients. Mitral valve prolapse (41 patients) was the most common cause of mitral insufficiency; the amount of valve insufficiency did not correlate with the leaflet involved or the severity of the prolapse. Patients with rheumatic disease either had combined mitral stenosis and insufficiency (27 patients) or pure mitral insufficiency (10 patients). Echocardiographic measurement of the mitral valve area separated patients with combined lesions from those with pure insufficiency. Fourteen patients had ruptured chordae tendineae; surgical findings were confirmatory in each patient who had valve replacement. Nineteen patients had left ventricular dysfunction; angiographic findings were confirmatory in each patient who underwent cardiac catheterization. Two dimensional echocardiographic findings reliably differentiated mitral insufficiency secondary to valve disease from that secondary to ventricular or papillary muscle dysfunction. Other causes of mitral insufficiency included mitral anular calcification (11 patients), idiopathic hypertrophic subaortic stenosis (5 patients), cleft anterior mitral leaflet (5 patients) and atrial myxoma (1 patient).

Mitral valve competence is dependent on normal and coordinated function of the mitral valve anulus, mitral valve leaflets, chordae tendineae, papillary muscles and left ventricular myocardium.[1] Because dysfunction of any one component of the mitral valve apparatus can lead to valve insufficiency, mitral regurgitation is a syndrome rather than a specific disease entity.[2] The diagnosis of mitral regurgitation may be readily made at the bedside; however, the etiologic diagnosis is often obscure.

Real time, two dimensional echocardiography facilitates study of the spatial and temporal relations of intracardiac structures and is a reliable diagnostic tool in a variety of cardiac disorders, particularly those of the mitral valve. In this study we evaluated the ability of two dimensional echocardiography to (1) differentiate among the anatomic causes of mitral insufficiency, (2) establish an etiologic diagnosis of mitral insufficiency, and (3) assess the frequency and relative incidence of each cause of mitral insufficiency.

Methods

Patients: During a 14 month period, 140 inpatients or outpatients were referred for two dimensional echocardiographic study because of a clinical diagnosis of mitral regurgitation. Each had an apical systolic murmur that was either holosystolic or late systolic in timing. The analysis of the two dimensional echocardiographic findings, cardiac catheterization data and surgical results of these patients constitute the basis of this report.

Two dimensional echocardiographic studies: These studies were performed using either a Grumman Health Systems RT-400 or a Varian V-3000 wide angle, phased array sector scanner. The illustrations presented are pho-

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lium-201 may influence the measured wall thickness but should not alter the geometric relation between the two scintigrams. In future studies external markers may be used to ensure superposition of the radioangiogram and thallium scintigram.

Background subtraction: Background subtraction of thallium activity is necessary to account for activity projected in the heart region that originates in the chest wall or lungs. The background levels vary from dog to dog and tend to mask perfusion defects because the percent difference between normal and abnormal tissue count levels decreases when a constant amount of activity is added to both areas. For example, when background radioactivity is half that in normally perfused myocardium, without background subtraction areas of myocardium with no perfusion would project activity levels that are one third of normal levels.

Narahara et al.[12] suggested that thallium activity in areas adjacent to the left ventricle overestimates actual background activity in the projection of the left ventricular area. However, no constant relation could be determined between true background activity and activity in areas contiguous with the left ventricle. Therefore, the mean value in contiguous areas was used as a measure of background activity because background subtraction both enhances the difference between normal and infarcted myocardium and attempts to correct for variation in background activity between dogs.

Thresholds and projections: The thresholds chosen for infarct definition in our method were those that yielded the best correlation with tissue data. As a result, the threshold was different for each of the two projections. A 20 percent threshold in the left lateral projection provided the best relation between scintigraphic and tissue infarct size whereas a 30 percent threshold level was required for the left anterior oblique projection. The relative increase in threshold for the left anterior oblique projection was apparently due to overlap of normal and infarcted tissue. Thus, in the left lateral projection maximal separation was achieved between normal myocardium and the infarcted tissue in the anterior wall and interventricular septum. However, in the left anterior oblique projection, there was more overlap of normal tissue from the posterior wall with the infarct area, resulting in increased count levels. This overlap also affects the simple regression line of best fit between scintigraphic and tissue infarct size because the regression line more closely approximates the identity relation in the left lateral projection (Fig. 5) than in the left anterior oblique projection (Fig. 6). Therefore, the lateral projection appears to be superior for identification of infarction due to occlusion of the left anterior descending coronary artery in dogs.

The differences encountered between scintigraphic and tissue measures of infarction may be due to several factors: (1) blurring of the edge of the defect in scintigrams due to myocardial motion; (2) masking of the edge of a defect by the activity of normal myocardium overlying the projection of the defect; (3) nonuniform wall thickness, which would alter the volume represented by a given scintigraphic myocardial area; (4) limitations in the finite resolution of the gamma camera; (5) nonuniform distribution of infarcted myocardium between the 5 mm slices from which measurements of infarct size were derived; and (6) definition of infarct size by NBT tissue staining, which differs from thallium scintigraphic infarct size because thallium defects may represent not only scar but also ischemia or metabolic abnormalities that affect the sodium-potassium (Na^+-K^+) pump.

Clinical implications: The computerized scintigraphic technique that we have developed provides a quantitative measure of infarct size for anterior infarction in the dog model in which infarct volumes are less than 15 percent of left ventricular myocardium. Its application to the analysis of normal myocardial scintigrams has not yielded false-positive results. Before this technique is applied clinically, additional studies should be performed. The optimal projection and threshold for analysis of infarct size with various infarct locations should be determined. On the basis of our results, it appears that the best projection for quantitation of infarct size will be one in which there is least overlap between normal and damaged myocardium. In this projection, application of 20 percent threshold may provide a useful measure of infarct size, but in other projections infarct size will be underestimated because overlying normal myocardium provides activity in the apparent region of damaged myocardium. For each of the left ventricular walls we assumed a constant relation between the endocardium, defined by the radioangiogram, and the epicardium, defined by the thallium scintigram. In patients this relation may be altered in the presence of chronic ischemic disease, previous infarction, myocardial hypertrophy or heart failure. A normal area, which serves as a standard for comparison of thallium activity levels, may not always be available in clinical situations with diffuse disease such as circumferential subendocardial infarction. Finally, the use of this technique in the clinical setting will require further corroboration by clinical and autopsy data.

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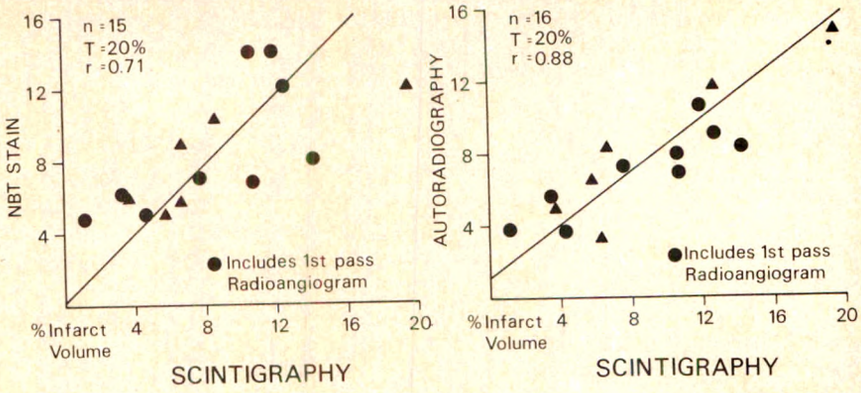

FIGURE 5. Relation of scintigraphic infarct size to tissue infarct size at 20 percent threshold level in the left lateral projection. Abbreviations as in Figure 3.

0.75 for thallium autoradiography and 0.71 and 0.70 for NBT tissue staining (Fig. 5 and 6).

The r *values obtained for the second observer were similar:* 0.88 and 0.76, respectively, for thallium autoradiography and 0.76 and 0.70 for NBT tissue staining, in the same scintigraphic projections. There was no significant difference (Student's *t* test) between paired infarct measurements by observers 1 and 2 in either the left lateral or left anterior oblique projection.

Control thallium scintigrams before coronary ligation: The threshold levels for the left lateral and left anterior oblique projections of 20 and 30 percent were used to analyze eight thallium scintigrams obtained before coronary ligation. The few pixels that had subthreshold counts were scattered along the left ventricular border and were therefore not considered to represent infarcted tissue. The mean and standard deviation of the percent of pixels with counts less than the infract thresholds were 0.7 ± 0.82 percent for the left lateral projection and 1.6 ± 1.3 percent for the left anterior oblique projection.

Discussion

Comparison with previous techniques: The method we have developed for analyzing thallium scintigrams was designed to reduce subjectivity in interpretation by minimizing errors by the observer in detection of an infarct edge. Thus, previous techniques[5–9] used for analysis of thallium scintigrams have depended on the observer's definition of an infarct edge. These results have greatly been influenced by display system capabilities, such as contrast enhancement, that affect visual interpretation of the infarct border. The use of such techniques by others has resulted in inconsistencies in quantitation of infarct size. Thus, although Wackers et al.[8] found a reasonably good correlation between infarct size by thallium scintigraphy and by NBT staining at postmortem study in patients who died with a large transmural infarct, Bulkley et al.[5] reported as much as a 10 percent variation among observers in definition of infarct size, and Henning et al.[7] were unable to correlate the size of perfusion defects with the extent of infarction as measured from serum creatine kinase curves.

The present technique provides a more objective basis for infarct definition from thallium scintigrams because the observer defines the left ventricular edge and normal areas whereas the computer defines the location and size of the infarct according to the distribution of radioactivity. Because the infarct causes a defect that may appear along the left ventricular border, detection of this missing edge is greatly enhanced by superimposing the left ventricular radioangiogram. The increased scatter of technetium-99m relative to thal-

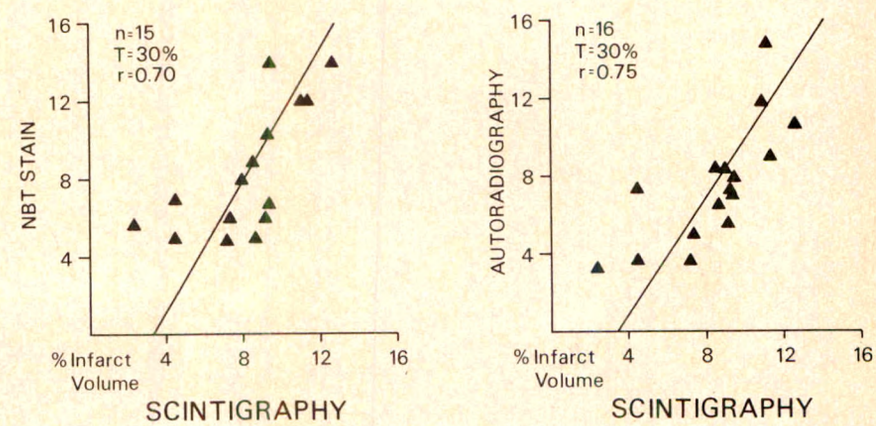

FIGURE 6. Relation of scintigraphic to tissue infarct size at 30 percent threshold level in the left anterior oblique projection. Abbreviations as in Figure 3.

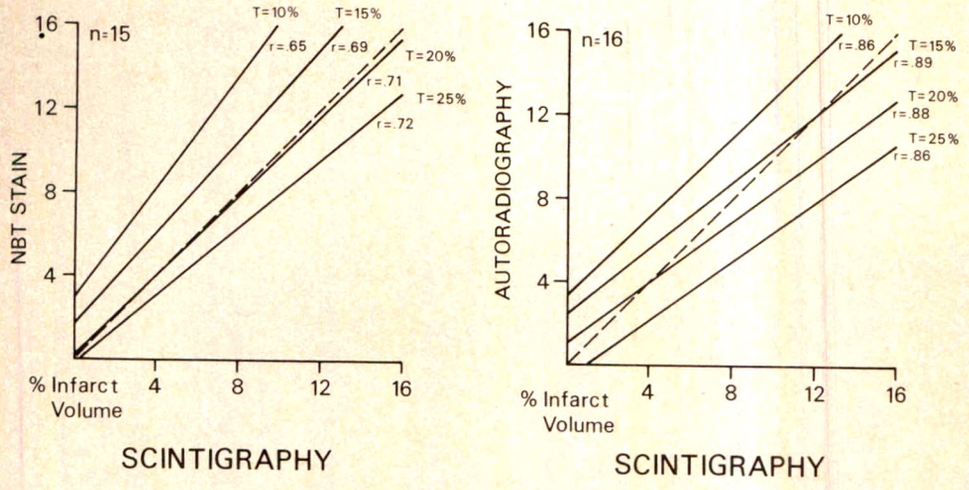

FIGURE 3. Effects of different threshold levels on relation of tissue infarct volume (nitro-blue tetrazolium [NBT] stain) to scintigraphic infarct size and autoradiography in the left lateral projection. **Solid lines** represent the regression relation for each threshold and **dashed lines** are lines of identity. n = number of dog studies; r = correlation coefficient; T = threshold level.

tetrazolium staining for dehydrogenase activity was performed with a solution consisting of 90 cc of sodium phosphate buffer (0.1 molar) at pH 7.2, 90 cc of sodium succinate and 30 mg of nitro-blue tetrazolium (NBT).[11] Nitro-blue tetrazolium stains revealed three zones within the myocardium: a normally stained subepicardial zone, a central zone that completely lacked stain and a subendocardial zone of partial staining. For estimating the extent of infarct, the two zones of depleted NBT stain were measured together.[10]

Thallium autoradiograms were obtained by opposing each tissue slice against a sheet of X-ray film for 7 days. Because thallium activity exposed the film, areas where thallium was not present appeared as nonexposed areas.[10] The areas of nonuptake of thallium were measured where the change in density was abrupt. The nonexposed areas were measured with planimetry and volumes of infarcted tissue in each 5 mm slice were calculated both from autoradiograms and from NBT stains by multiplying the infarct area of the slice by the distance between the slices (5 mm). This tissue volume technique assumes a uniform distribution of infarcted tissue within each 5 mm slice. The total infarct volume was derived from the sum of infarct volumes for all 5 mm slices. The percent of infarct volume was calculated as the total infarct volume divided by the total volume of left ventricular myocardium, which was determined from its weight and specific gravity. Specific gravity was calculated from the weight of a known volume of myocardium.

Results

Comparison of tissue and scintigraphic infarct size: The results for different threshold levels in the left lateral and left anterior oblique projections shown in Figures 3 and 4 are based on ventricular and background areas defined by observer 1. Results in the left lateral projection include nine dog studies in which the left ventricular border of the thallium scintigram was defined with the aid of radioangiographic blood pool contours. On the basis of the criteria of best correlation and near identity relation with both tissue measurements of infarction, threshold levels of 20 and 30 percent were chosen for the left lateral and left anterior oblique views, respectively. The correlation coefficients relating tissue and scintigraphic infarct size for the first observer at these threshold levels in the left lateral and left anterior oblique projections, respectively, were 0.88 and

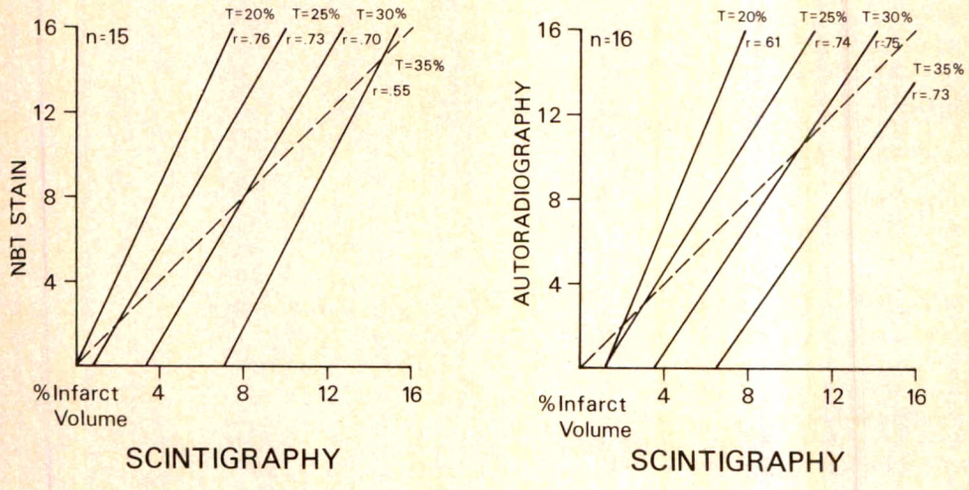

FIGURE 4. Effects of different threshold levels on relation of tissue infarct volume (NBT stain and autoradiography) to scintigraphic infarct size (autoradiography) in the left anterior oblique projection. Abbreviation as in Figure 3.

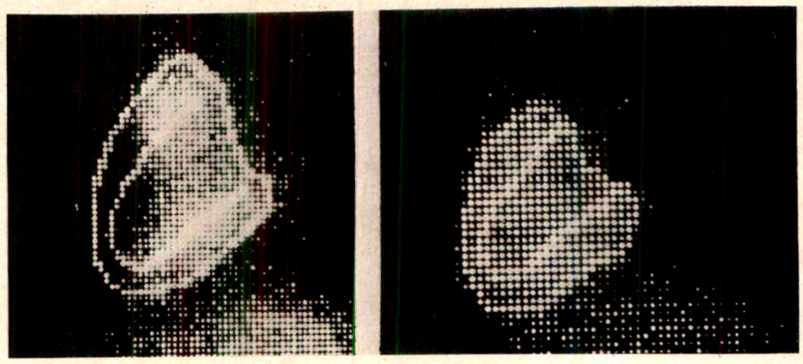

FIGURE 1. Superimposition of thallium-201 scintigram and technetium-99m pyrophosphate radioangiogram in the left lateral projection. Preinfarction (**right**) and postinfarction (**left**) thallium scans with endocardial and epicardial borders highlighted.

anterior oblique projection, then in the left lateral view. A Picker 3-C scintillation camera equipped with a high resolution parallel hole collimator was used to accumulate mercury X rays. The gamma camera was adjusted for a preset time of 10 minutes during which at least 300,000 counts were accumulated in each view. In 9 of the 16 dogs a 15 mCi bolus of technetium-99m pyrophosphate was injected through the jugular venous catheter after the last thallium image was recorded and before the dog and gamma camera were moved, in order to produce a radioangiogram. All scintigraphic data were stored on a Panasonic videotape storage system for later processing by a Hewlett-Packard 5407A scintigraphic data analyzer.

Tissue data accumulation: The dogs were sacrificed after scintigraphy. The heart was removed and the ventricular portion was sectioned for processing by thallium-201 autoradiography and nitro-blue tetrazolium (NBT) staining. The methods for these procedures have been described elsewhere in detail.[10] In brief, serial sections averaging 20 μ in thickness were obtained with a Leitz 1400 heavy duty microtome sledge. Sectioning was begun at the left ventricular apex and was continued to a point 1 to 2 cm proximal to the site of coronary ligation in an effort to include all of the infarcted myocardium. Samples were obtained at 5 mm intervals throughout the specimen which resulted in the sampling of 8 to 10 sites in each dog heart.

Scintigraphic analysis: To enhance definition of left ventricular walls in the left lateral thallium scintigram, an ungated radioangiogram of the first pass of technetium-99m pyrophosphate through the left ventricle was recorded in nine dogs. Because the positions of dog and camera and the computer parameters for framing of data were identical for the thallium-201 scintigram and the radioangiogram, the images were superimposed (Fig. 1) and traced with a light pen. The perimeter of the thallium scintigram was taken to represent the epicardial surface and the perimeter of the blood pool the endocardial surface of the left ventricle. For each major segment of left ventricular wall (anterior, posterior or apex), wall thickness was assumed to be uniform, enabling the operator to reconstruct the missing epicardial edge in areas of thallium-201 perfusion defects. The apex was usually thinner than the other two walls.

The computer-processed scintigrams were partitioned into a 128 by 128 matrix of elements and were analyzed independently by two observers. Each element, referred to as a pixel, represented an area of approximately 2 by 2 mm and two groups of pixels were defined in the thallium-201 scintigram (Fig. 2). Group I, just outside the border of the left ventricular silhouette, was selected to represent background radioactivity in the lungs and chest wall. This activity was also present in the left ventricular area. To correct for the activity in this overlying tissue, the average number of counts per pixel in group I was determined and that value was subtracted from the counts of all pixels within the left ventricular silhouette. Group II, selected to represent normal myocardial tissue, was defined as a strip approximately 1 cm wide near the basal left ventricular border remote from the area of perfusion defect. The left ventricular perimeter was defined after background subtraction with no additional image processing.

The average number of counts per pixel in group II was used as a standard for comparing counts in the left ventricular area. Pixels in the left ventricular region that had count levels less than a given percent (threshold) of the average level in group II and that were not scattered along the left ventricular border were considered to represent infarcted tissue. The total number of pixels included as infarcted tissue for each 5 percent increment of threshold level, from 0 to 100 percent, was calculated by the computer. Scintigraphic infarct size at a given threshold level was calculated as the total number of pixels with subthreshold counts divided by the total number of pixels in the left ventricular region. The correlation between tissue and scintigraphic infarct size measurements was calculated at each threshold level to determine the threshold level that had the best fit with the tissue data.

The computer analysis of scintigrams, including the tracing of silhouettes and the selection of background and normally perfused areas, was performed by two independent observers and their results were compared statistically.

Tissue data analysis: Adjacent sections were obtained for thallium autoradiography and for NBT staining.[10] Nitro-blue

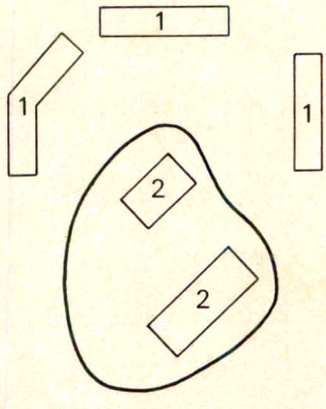

FIGURE 2. Identification of areas for computer analysis of thallium-201 scintigrams. 1 = lung background; 2 = normal left ventricle.

Quantification of Thallium-201 Scintigrams in Acute Myocardial Infarction

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A method has been developed for measurement of myocardial infarct size from thallium-201 scintigrams that depends on computer measurement of levels of radioactivity in the myocardium. In 16 dogs, thallium-201 scintigrams were obtained in the left lateral and left anterior oblique projections 48 hours after ligation of the left anterior descending coronary artery. Scintigraphic results were obtained by two independent observers and were compared with tissue measurements of infarct volume calculated from thallium autoradiograms and nitro-blue tetrazolium (NBT)-stained tissue slices. Infarct volumes derived from tissue measurements were used to develop criteria for the computer scintigraphic technique. There was no significant difference in the scintigraphic measurements made by the two observers. Scintigraphic infarct size in the left lateral and left anterior oblique projections correlated with tissue infarct size with *r* values of 0.88 and 0.75, respectively, for thallium autoradiography and 0.71 and 0.70, respectively, for NBT tissue staining. The range of infarct volume was 3.3 to 14.8 percent of the left ventricular mass. Results of this study suggest that scintigraphic quantitation of infarct size is feasible in this dog model.

The importance of quantitating infarct size stems from findings that in both acute and chronic myocardial infarction, morbidity and mortality are related to the extent of myocardial damage.[1] In addition, various therapeutic interventions have been proposed that may limit infarct size[2] and possibly improve the patient's chances for survival. The techniques used to quantitate infarct size—precordial mapping of electrocardiograms[3] and measurement of serum enzyme activity[4]—have limitations. As a result, the development of scintigraphic methods is of considerable interest. The techniques used to detect or quantitate the size of perfusion defects from thallium-201 scintigrams have involved visual interpretation.[5–9] These techniques cannot readily be applied by other investigators because of differences in observers' definition of infarct borders and because of limitations in contrast enhancement attainable with standard display systems. The purpose of our study was to develop quantitative criteria for detecting the myocardial infarct area in computer-processed thallium-201 scintigrams and to validate these measurements by comparisons with the volume of infarcted tissue.

Methods

Experimental preparation and scintigraphic data accumulation: Myocardial infarction was produced in 16 adult mongrel dogs by serial ligation of branches of the left anterior descending coronary artery. Branches supplying the left ventricular free wall were ligated beginning 1.5 cm distal to the origin of the left anterior descending artery. The ligations proceeded serially until there was gross evidence of infarction, including epicardial bulging and color change.

At 1 or 2 weeks before infarction and at 48 hours after infarction, 2 mCi of thallium-201 was injected through a jugular venous catheter. Ten minutes after the administration of thallium, scintigrams were obtained first in the 30° left

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conscious dogs by Tomoike et al.[12] who suggested that propranolol improved myocardial function by causing a more favorable distribution of blood flow within the ischemic myocardium. Whether bevantolol offers a distinct advantage over propranolol cannot be answered by our study, although there are obvious clinical situations, for example, bronchial asthma, in which a cardioselective agent may have a favorable theoretical basis. Finally, our results suggest that, in addition to reducing myocardial oxygen demands, certain beta adrenergic blocking agents may also reduce myocardial ischemia by improving transmural blood flow distribution. That these agents may work more effectively in patients with some anterograde flow in partially obstructed vessels is suggested by the work of Gold et al.[29] and by our results obtained in animals.

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ischemic endocardial/epicardial ratio would therefore increase.

Taking a still different perspective, the results of a recent study[9] have suggested that myocardial blood flow distribution can only occur if both cardiac beta$_1$ receptor and coronary vessel beta$_2$ receptor blockade are achieved simultaneously. Berdeaux et al[9] found that the beta adrenergic blocking agents dl-propranolol and dl-pindolol were able to induce blood flow redistribution whereas dl-practolol proved ineffective. D-propranolol exerted no influence on blood flow, thereby establishing a basic requirement for beta blockade. All three beta blocking agents induced bradycardia; thus the negative chronotropic property was eliminated as the sole explanation for a redistribution of blood flow. Because it has already been established that, like practolol, the cardioselective beta$_1$ blocking agent atenolol failed to improve the ischemic endocardial/epicardial ratio, the need for nonselective beta antagonism was implied.[4] It was suggested that the blockade of beta$_2$ receptors by propranolol resulted in an "unmasking" of alpha adrenergic vasoconstrictor receptors in subepicardial layers to the effects of circulating catecholamines, which increased vascular resistance relative to the subendocardium with its scarcity of alpha receptors.[25] Blood flow would therefore be redistributed to the subendocardium. Practolol, atenolol and other cardioselective inhibitors, by leaving beta$_2$ vasodilator receptors unblocked to counter alpha receptor-mediated vasoconstriction, would not be expected to increase flow to the deeper layers of the ischemic myocardium. In contrast, Marshall and Parratt[3] suggested that alpha adrenergic stimulation might actually decrease blood flow by constricting large vessels in the ischemic region; this hypothesis suggests that a cardioselective agent such as practolol or bevantolol may offer an advantage over a nonselective agent such as propranolol.

Our comparison of bevantolol, practolol and propranolol demonstrates that the increased endocardial/epicardial ratio observed after beta receptor blockade is most likely not associated with an unmasking of alpha adrenergic receptors in the coronary bed, although this cannot be ruled out completely. More likely, an increase in diastolic perfusion time probably exerts the greatest influence on blood flow redistribution. Previous data[19,26] have shown that subendocardial blood flow in a maximally dilated ischemic region could be accurately predicted by diastolic pressure-time index. Because stenosis of the left circumflex coronary artery abolished reactive hyperemia in our study, it is probable that the subendocardial arterioles in the distal vascular bed were maximally vasodilated and critically dependent on the diastolic pressure-time index. In contrast, because the level of subepicardial blood flow during partial coronary occlusion is nearly normal and capable of autoregulating to changes in myocardial oxygen consumption, blood flow to the superficial layers of both nonischemic and ischemic regions is primarily dependent on the chronotropic and inotropic state of the heart. A strong correlation is therefore suggested between the effects of beta antagonists on heart rate and contractility and the ability of these agents to increase the ischemic endocardial/epicardial flow ratio significantly. Why only bevantolol increased subendocardial blood flow in the ischemic region is not readily apparent from our results. Changes in myocardial wall tension and heart size may have contributed to the differences observed between these three agents, but these factors were not evaluated in our study.

Effects on contractile function: The differential effects of the three beta adrenergic antagonists on contractility can be discussed in terms of regional and global function. Results obtained by use of Walton-Brodie strain gauge arches to measure regional contractility must be interpreted with caution. These gauges have been shown[18] to be affected by changes in muscle fiber stretch due to alterations in preload and afterload. Because no significant changes occurred in left ventricular end-diastolic pressure (Table I) after administration of any of these agents it is unlikely that changes in preload were responsible for the differential effects seen. In addition, the magnitude of the decreases in afterload did not appear to correlate with changes in regional contractility. Thus, although changes in fiber stretch in the left ventricular wall may have contributed artifacts to the differential effects of the three beta receptor blocking agents these forces do not appear to have been of major importance. However, changes in ischemic contractile function seemed to reflect mainly alterations in subendocardial blood flow. Although it is not known precisely which fibers are contributing to the responsiveness of the strain gauges, previous work[17,27,28] has shown that gauges attached with deep sutures or pins and oriented perpendicular to the base-apex axis of the heart primarily reflect subendocardial muscle function. That contractility in the ischemic region decreased concomitantly with a selective depression of subendocardial flow (control state) and increased after a rise in subendocardial perfusion (bevantolol) supports this suggestion.

In addition to regional contractility important differences also existed concerning the effects of the three beta blocking agents on heart rate, mean aortic pressure and overall left ventricular function (nonischemic contractile force, tension-time index). Propranolol produced the largest decrease in heart rate, mean aortic pressure and overall left ventricular function (nonischemic contractile force, tension time index). This may have been due to the direct cardiac depressant properties of propranolol,[11] which are not shared by practolol[14] or bevantolol.[15] Practolol, a cardioselective beta antagonist with intrinsic sympathomimetic properties,[14] produced the least depression in heart rate and left ventricular function; however, the importance of the intrinsic activity of practolol in preventing cardiac depression cannot be ascertained from this study.

Clinical implications: Because of differences in species, anesthesia, surgery and the resultant high sympathetic tone, the results of our study cannot be extrapolated to man. However, these results obtained with bevantolol are similar to those of previous work in

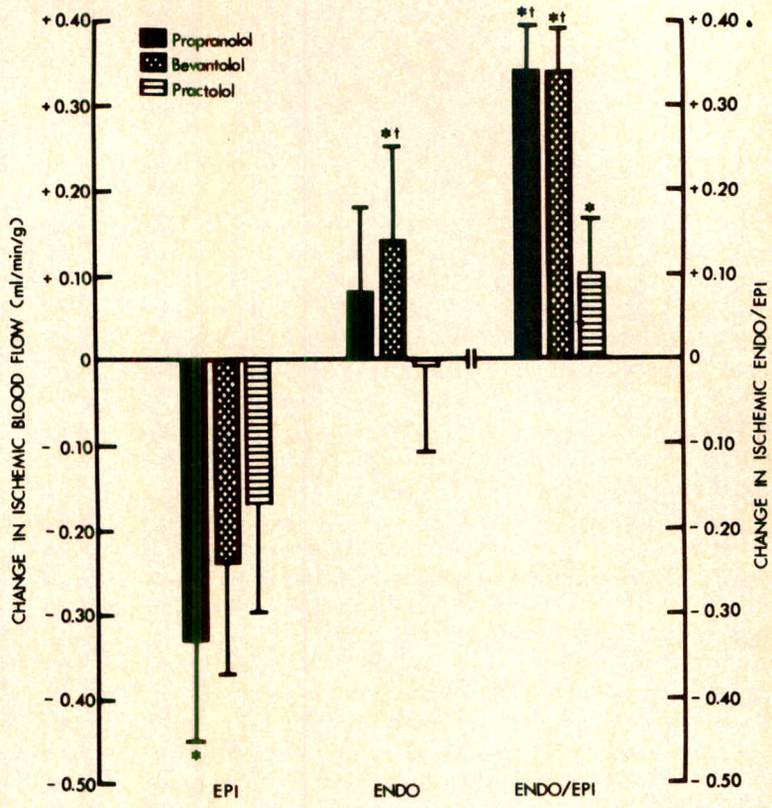

FIGURE 2. Effect of propranolol (0.3 mg/kg, intravenously), bevantolol or practolol (1.0 mg/kg, intravenously) on ischemic blood flow and endocardial/epicardial ratio, expressed as change from control value. Values are the mean and standard error of eight experiments with bevantolol or practolol and six experiments with propranolol. * = significantly different from control ($P < 0.05$); † = significantly different from practolol ($P < 0.05$); Endo = endocardial; Epi = epicardial; Endo/Epi = endocardial/epicardial blood flow ratio.

pathomimetic activity,[15] results in a favorable redistribution of flow within an ischemic region of the myocardium. The increase in subendocardial blood flow in this area plus an overall reduction in myocardial oxygen demand (due to decreases in heart rate, dP/dt and tension-time index) produced by bevantolol indicates an improvement in the oxygen supply-demand balance in the ischemic myocardium. The increase in subendocardial contractile function produced by bevantolol also suggests a lessening of ischemia in this area. Beta$_1$ receptor blockade produced by practolol and a combined beta$_1$ and beta$_2$ receptor blockade produced by propranolol also resulted in a redistribution of blood flow within the ischemic myocardium; however, the increase in endocardial/epicardial blood flow ratio reflected primarily decreases in subepicardial flow and cannot be regarded as beneficial. No improvement in contractile function occurred after either agent. Further comparative studies in conscious dogs and man are needed to determine if these favorable actions of bevantolol are peculiar to the anesthesized animal.

Mechanisms for flow redistribution: Beta receptor antagonists have been found therapeutically effective in alleviating symptoms of angina pectoris.[1] The results of our study and others[5,8] have shown that these agents are also helpful in preserving the myocardium from further insult by redistributing coronary blood flow within or to areas of ischemia. Several mechanisms have been proposed that could account for this phenomenon.

An increase in diastolic perfusion time during bradycardia has been critically important in restoring blood flow to the ischemic subendocardium.[7] Blockade of beta$_1$ myocardial receptors would therefore exert a beneficial effect on redistributing blood flow to ischemic subendocardial layers by a resultant reduction in heart rate. This mechanism has been favored in investigations of the effects of propranolol and practolol on increasing flow to normal or ischemic areas of the canine myocardium, effects that are partially abolished by atrial pacing.[3,6] However, not all studies have found a significant correlation between heart rate and an increased endocardial/epicardial ratio or ischemic blood flow.[5,8] Vatner *et al.*[5] found an increase in ischemic blood flow in conscious dogs with minimal change in heart rate.

The differential effects of a reduced myocardial oxygen consumption on resistance vessels of the subepicardium and subendocardium in ischemic areas produced by a decrease in heart rate and myocardial contractility may be primarily responsible for the increase in the endocardial/epicardial ratio seen after beta blockade. According to Gross and Winbury,[6] the subendocardium has less arteriolar dilator reserve for maintaining flow than does the subepicardium during conditions of myocardial ischemia. When oxygen consumption decreases and myocardial metabolism subsequently slows after beta adrenergic blockade, then coronary vessel resistance should selectively increase in the subepicardium because of autoregulation, shifting the flow to subendocardial areas of less resistance. The

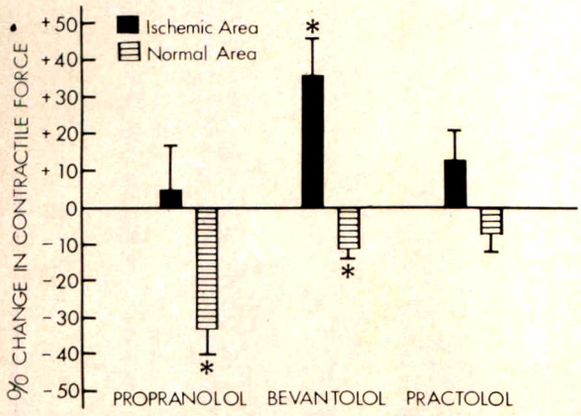

FIGURE 1. Effect of propranolol (0.3 mg/kg, intravenously), bevantolol or practolol (1.0 mg/kg, intravenously) on nonischemic and ischemic myocardial contractile force, expressed as percent change from the control value. Values are the mean and standard error of the mean for eight experiments with bevantolol or practolol and six experiments with propranolol. * = significantly different from control value ($P < 0.05$).

dial contractile force in the normal and ischemic regions of the myocardium. Propranolol (−33 percent) and bevantolol (−11 percent) produced significant decreases in contractile force in the normal area whereas practolol produced no change. However, only bevantolol (+36 percent) produced a significant increase in contractile force in the ischemic region.

Regional myocardial blood flow: The effects of propranolol, practolol and bevantolol on tissue blood flow (assessed with microspheres) are summarized in Table II and Figure 2. After beta blockade by all three compounds, blood flow to normal areas decreased significantly ($P < 0.05$) in both subepicardial and subendocardial layers, leaving the endocardial/epicardial ratio unchanged. However, propranolol significantly ($P < 0.05$) decreased subepicardial flow in the ischemic region whereas subendocardial blood flow was maintained, which resulted in an increased endocardial/epicardial flow ratio. Practolol also increased the ischemic endocardial/epicardial ratio, but this effect was significantly less than that seen after propranolol or bevantolol (Fig. 2). In contrast, bevantolol selectively increased subendocardial flow in the ischemic region whereas subepicardial flow showed a small decrease. These changes also resulted in a significant increase in the endocardial/epicardial ratio of the ischemic myocardium.

Discussion

This dog model developed to produce regional myocardial ischemia differs from others[3,5,23] in which beta adrenergic blocking agents were studied after total coronary arterial occlusion but resembles that of Tomoike et al.,[12] who studied the effect of propranolol in a partial coronary occlusion model in conscious dogs. We believe that our model more accurately resembles the clinical situation in angina pectoris in which regional coronary flow is limited and a stable area of hypofunction exists. In addition to this study, previous control experiments performed in our laboratory[15,24] demonstrated the stability of a left circumflex coronary stenosis of a similar severity over a 30 to 120 minute period.

Myocardial blood flow redistribution and contractile function after cardioselective beta receptor blockade: This study indicates that beta receptor blockade produced by bevantolol, a new cardioselective beta adrenergic blocking agent without intrinsic sym-

TABLE II

Comparative Effects of Propranolol (no. = 6), Practolol (no. = 8) and Bevantolol (no. = 8) on Regional Myocardial Blood Flow During Stenosis of the Left Circumflex Coronary Artery

Region	Control Value	Propranolol	Practolol	Bevantolol
LV anterior (normal)				
Epicardium (ml/min per g)	1.36 ± 0.17*	0.86 ± 0.17†	1.13 ± 0.10†	0.81 ± 0.15†
Endocardium (ml/min per g)	1.53 ± 0.15	0.97 ± 0.17†	1.26 ± 0.12†	0.93 ± 0.15†
Transmural (ml/min per g)	1.44 ± 0.14	0.91 ± 0.17†	1.19 ± 0.11†	0.87 ± 0.15†
Endo/Epi	1.14 ± 0.04	1.18 ± 0.06	1.12 ± 0.02	1.18 ± 0.06
LV posterior (ischemic)				
Epicardium (ml/min per g)	1.08 ± 0.14	0.75 ± 0.14†	0.91 ± 0.12	0.84 ± 0.13
Endocardium (ml/min per g)	0.64 ± 0.15	0.73 ± 0.20	0.63 ± 0.14	0.77 ± 0.13†
Transmural (ml/min per g)	0.86 ± 0.12	0.74 ± 0.18	0.77 ± 0.12	0.81 ± 0.14
Endo/Epi	0.59 ± 0.05	0.93 ± 0.09†‡	0.69 ± 0.10†	0.93 ± 9.09†‡

* Values are expressed as mean value ± 1 standard error. Control values for the three groups were found not to be significantly different by analysis of variance and were pooled for comparison of drug effects.
† Significantly different from control value ($P < 0.05$).
‡ Significantly different from practolol ($P < 0.05$).
Endo/Epi = endocardial/epicardial blood flow ratio; LV = left ventricle.

Propranolol shifted the chronotropic dose-response curve to isoproterenol (beta$_1$ receptors) to the right (16.0 ± 1.8). The decrease in diastolic peripheral blood pressure signifying beta$_2$ receptor stimulation was similarly shifted. Practolol (12.3 ± 2.2) and bevantolol (12.5 ± 2.0) produced a similar inhibition to that of propranolol on isoproterenol-induced increases in heart rate but showed minimal effects on diastolic blood pressure. The shifts produced by practolol and propranolol were similar to the shifts reported by Marshall and Parratt[3] and Pearle et al.[19] in studying differences in these drugs during acute ischemia.

Analysis of left ventricular tissue samples: After completion of the experiment, the left circumflex coronary artery was ligated, and 1 ml of India ink injected distal to the ligation at the mean arterial blood pressure of the dog to darken the area of myocardium subjected to the stenosis. The heart was excised, washed with saline solution and fixed in 10 percent formalin for 24 hours. The left ventricle was sectioned into base, middle and apex of both anterior (area perfused by the left anterior descending artery) and posterior (area perfused by the left circumflex artery) regions. These samples were subdivided into subepicardial (outer) and subendocardial (inner) layers of approximately equal weight (2 to 3 g). All 12 tissue samples were weighed and placed in glass scintillation vials, and the activity of the isotopes in each tissue sample was determined at two energy windows in an autogamma spectrometer (Searle Analytic 1195). The activity of each isotope in the reference blood flow sample was determined in a similar manner.

The true activity of each isotope in the tissue sample was separated by a preprogrammed computer and myocardial blood flow (Q_m) calculated from the equation:

$$Q_m = Q_r \cdot Cm/C_r,$$

where Q_r is the rate of withdrawal of the reference blood sample, C_r is the activity (counts/min) of the reference blood sample, and C_m is the activity (counts/min per g) of the myocardial tissue sample. The tissue areas of the base, middle and apex were pooled for calculation of tissue blood flow in the subepicardium and subendocardium of the nonischemic and ischemic regions. Transmural blood flow was the weighted average obtained from the subepicardium and subendocardium of the nonischemic or ischemic region of each heart.

Calculation of indexes: The tension-time index (TTI) was calculated by determining the area under the aortic systolic blood pressure curve and multiplying by heart rate.[20] The diastolic pressure-time index (DPTI) was calculated by determining the area between the aortic and left ventricular end-diastolic pressure curves and multiplying by heart rate.[21] The areas were calculated by planimetry. The ratio of DPTI/TTI was used as an index of cardiac oxygen balance.

Data analysis: Transmural distribution of coronary blood flow was expressed as the ratio of counts per gram of subendocardium to counts per gram of subepicardium (endocardial/epicardial ratio). Tissue blood flow was expressed in ml/min per g. Statistical analysis among groups was made by analysis of variance, with individual comparisons performed using Dunnet's modification of the t test.[22] Differences between endocardial/epicardial ratio and hemodynamic data were considered significant when the probability (P) value was <0.05.

Results

Control series: Adjustments with the occluder were necessary during the first 30 minutes of left circumflex coronary arterial stenosis. However, in the four dogs treated with saline solution, no significant changes in hemodynamics and ischemic transmural blood flow (endocardial/epicardial ratio 0.64 ± 0.07 to 0.66 ± 0.06) occurred between 30 and 60 minutes, which indicates the stability of the stenosis during this time. These results are in agreement with previous data from this laboratory.[15]

Hemodynamic effects of propranolol, practolol and bevantolol (Table I): All three compounds produced significant (P <0.05) decreases in heart rate and tension-time index. In addition, propranolol and bevantolol produced significant (P <0.05) decreases in mean aortic pressure, left ventricular systolic pressure and dP/dt. Propranolol produced significantly greater (P <0.05) decreases in heart rate, mean aortic pressure and the tension-time index than did practolol and bevantolol. The overall subendocardial oxygen supply-demand balance, as reflected by the ratio of the diastolic pressure-time index to tension-time index, was increased significantly by all three beta adrenergic blocking agents.

The results shown in Figure 1 summarize the effect of the beta adrenergic blocking agents on subendocar-

TABLE I

Comparative Hemodynamic Effects of Propranolol (no. = 6), Practolol (no. = 8) and Bevantolol (no. = 8) During Stenosis of the Left Circumflex Coronary Artery

	Control Value	Propranolol	Practolol	Bevantolol
Heart rate (beats/min)	174 ± 5*	136 ± 7†‡	146 ± 4†	143 ± 8†
Mean aortic blood pressure (mm Hg)	123 ± 3	101 ± 4†‡	118 ± 3	108 ± 5†
Left ventricular systolic pressure (mm Hg)	145 ± 4	121 ± 5†	141 ± 5	123 ± 5†
Left ventricular end-diastolic pressure (mm Hg)	5 ± 3	7 ± 4	5 ± 4	5 ± 3
dP/dt max (mm Hg/sec)	2488 ± 106	1500 ± 182†	2214 ± 190	1731 ± 171†
Ischemic coronary blood flow (ml/min)	27 ± 2	25 ± 5	21 ± 3	29 ± 4
Tension-time index (TTI) (mm Hg/sec per min)	3821 ± 123	2430 ± 114†‡	3396 ± 185†	2983 ± 171†
Diastolic pressure-time index (DPTI) (mm Hg/sec per min)	4647 ± 125	4091 ± 217	4695 ± 185	4895 ± 225
DPTI/TTI	1.24 ± 0.08	1.70 ± 0.11†	1.43 ± 0.11†	1.67 ± 0.10†

* Values are expressed as mean value ± 1 standard error. Control values for the three groups were found not to be significantly different by analysis of variance and were pooled for comparison of drug effects.
† Significantly different from control group (P <0.05).
‡ Significantly different from practolol and bevantolol (P <0.05).
dP/dt max = maximal rate of rise of left ventricular pressure.

of myocardial ischemia without a concomitant change in endocardial/epicardial ratio. Recently, using radioactive microspheres, Berdeaux et al. found[9] that propranolol increased blood flow to ischemic regions of the myocardium and increased endocardial/epicardial ratio whereas practolol showed no such effect. These authors[9] concluded that cardioselective beta adrenergic blocking agents do not produce a favorable redistribution of coronary flow to ischemic myocardium. In contrast, previous work of Marshall and Parratt[3] suggested an advantage of cardioselective beta blockade on ischemic blood flow.

Another area of controversy concerns the effect of different beta adrenergic blocking agents on global or regional myocardial contractile function. The effects of oral doses of propranolol and practolol on left ventricular function in the awake dog were recently shown to be nearly identical.[10] Propranolol was shown to improve myocardial dysfunction in the ischemic heart of conscious dogs.[5,11,12] Other studies[13] indicated that propranolol depressed contractile function in awake dogs whereas practolol did not. However, few studies have compared equivalent beta receptor blocking doses of cardioselective versus noncardioselective agents. Therefore, this investigation was designed to compare practolol, a cardioselective beta adrenergic antagonist with intrinsic sympathomimetic properties,[14] with bevantolol, a cardioselective agent that lacks intrinsic activity,[15] on distribution of blood flow and contractile function in the ischemic myocardium. Propranolol, a nonselective beta antagonist, was studied for purposes of comparison.

Methods

Experimental preparation: Adult mongrel dogs of either sex, weighing 15 to 25 kg were fasted overnight, anesthetized with intravenously administered sodium pentobarbital (30 mg/kg body weight) and ventilated with a respirator (Harvard model 607) with room air at 10 to 15 breaths/min. Atelectasis was prevented by maintaining an expiratory pressure of 5 to 7 cm of water with a trap. Arterial blood pH was maintained between 7.35 and 7.45 by adjusting the respirator and by intravenous infusion of 1.5 percent sodium bicarbonate when necessary. Rectal temperature was monitored and maintained at 37.5 ± 1° C (mean ± standard error of the mean) by a heating pad and servomechanistic controller.

Mean arterial blood pressure was recorded by means of a catheter inserted into the right femoral artery, advanced to the thoracic aorta and attached to a strain guage pressure transducer (Statham P23AC). The right femoral vein was catheterized for drug administration and the left femoral artery was catheterized for withdrawal of reference arterial blood samples used in determining myocardial tissue blood flow. Left ventricular systolic and end-diastolic pressures were determined by means of a calibrated pressure transducer-tipped catheter (Millar PC380 no. 8F) passed through the left carotid artery into the left ventricle. The first derivative of left ventricular pressure (dP/dt) was obtained by electronic differentiation of the left ventricular pressure pulse.

Thoracotomy was performed at the left fifth intercostal space with the lung gently retracted and the heart suspended in a pericardial cradle. A 1.0 to 1.5 cm segment of the left circumflex coronary artery was dissected from surrounding tissue near its origin, and a calibrated flow probe (Statham SP 7515) placed around the vessel. Coronary blood flow was recorded by use of an electromagnetic flowmeter (Statham 2202). A micrometer-driven, mechanical vessel occluder[16] was placed distal to the probe so that no branches were present between the probe and the occluder. The occluder was used to determine zero blood flow and to produce coronary arterial stenosis.

Myocardial contractile force of the area perfused by the left anterior descending (nonischemic) and left circumflex (ischemic) coronary artery was determined by two Brodie-Walton strain gauge arches. The gauges were attached to the left ventricular wall with deep sutures (9 to 10 mm) and oriented perpendicular to the base-apex axis of the heart. Gauges attached in this manner have previously been shown to reflect primarily changes in contractility of the subendocardium.[17] In addition, gauges oriented in this manner have been demonstrated to be less susceptible to changes in preload and afterload.[18] The gauges were stretched to approximately 140 percent of their initial length and the responsiveness of each gauge was tested by an intravenous injection of isoproterenol (0.3 μg/kg). Changes in contractile force were expressed as percent of control.

A catheter was placed in the left atrium by way of the atrial appendage for injection of tracer microspheres. Heparin (500 units/kg intravenously) was administered. The electrocardiogram (limb lead II), phasic and mean aortic blood pressure, left ventricular systolic and end-diastolic pressures, dP/dt, contractile force in normal and ischemic regions and phasic and mean coronary blood flow were continuously recorded on a polygraph (Grass 7).

Regional myocardial blood flow: The distribution of coronary blood flow was determined using the radioactive microsphere technique. Carbonized plastic microspheres (15 ± 3 μ diameter, 3M Company) labeled with either cerium-141 (8.55 mCi/g) or strontium-85 (12.24 mCi/g) were obtained as 2 mCi of nuclide in 10 ml of isotonic saline solution to which 1 drop of of Tween 80® was added to minimize aggregation. The mixture was agitated before injection in a vortex mixer (Cole-Parmer 4722) for 15 minutes. Approximately 2 to 4 × 10^6 spheres were injected into the left atrium in a total volume of 0.75 to 1.0 ml followed by an 8 ml saline (37° C) wash. A few seconds before each microsphere injection, a timed collection of reference flow from the femoral artery was started and maintained at a constant rate (7 ml/min) for 3 minutes. The total number of microspheres of each type injected was selected to provide a sphere density of at least 400 spheres/tissue sample.

Experimental design: After operation the preparation was allowed to stabilize for 30 minutes. Two experimental groups (practolol and bevantolol) of eight dogs each and one group (propranolol) of six dogs were completed. An additional control group of four animals received saline solution. In each group a stenosis of the left circumflex coronary artery sufficient to abolish reactive hyperemia and reduce resting coronary blood flow and contractile force in the ischemic region 30 to 40 percent was produced by the mechanical occluder. Another 30 minutes of observation was then required to ensure the stability of the stenosis. In each group of experiments, microspheres were injected during a control period and 30 minutes after intravenous administration of either saline, propranolol (0.3 mg/kg), practolol (1.0 mg/kg) or bevantolol (1.0 mg/kg).

The effectiveness of each drug in antagonizing chronotropic responses to various doses of isoproterenol (0.03 to 10 μg/kg intravenously) was tested at the end of each experiment (40 minutes after administration of each beta blocking agent).

Comparative Effects of Cardioselective Versus Noncardioselective Beta Blockade on Subendocardial Blood Flow and Contractile Function in Ischemic Myocardium

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The comparative effects of three beta adrenergic antagonists, bevantolol (CI-775, a new cardioselective agent), practolol and propranolol, on regional myocardial blood flow and contractile function distal to a severe flow-limiting stenosis of the left circumflex coronary artery were studied in the anesthetized dog. Equivalent beta$_1$ receptor blocking doses of each agent were administered 30 minutes after production of a stenosis sufficient to reduce resting coronary blood flow and contractile force approximately 40 percent. Regional myocardial blood flow and contractile force were measured with radioactive labeled microspheres and Brodie-Walton strain gauge arches, respectively. After treatment with propranolol (0.3 mg/kg), subepicardial flow in the ischemic area decreased significantly whereas subendocardial flow was maintained, resulting in an increased endocardial/epicardial blood flow ratio (0.59 ± 0.05 to 0.93 ± 0.09) (mean ± standard error of the mean). No significant change was observed in contractile performance of the ischemic area. Practolol (1.0 mg/kg) also produced a significant increase in endocardial/epicardial ratio (0.59 ± 0.05 to 0.69 ± 0.10) in the ischemic myocardium. Contractile performance remained unchanged. In contrast, after treatment with bevantolol (1.0 mg/kg), subendocardial flow (0.64 ± 0.13 to 0.77 ± 0.13 ml/min per g) and contractile function increased significantly (36.0 ± 11.0 percent) in ischemic myocardium. A marked increase in endocardial/epicardial ratio (0.59 ± 0.05 to 0.93 ± 0.09) was also observed.

These results suggest that a redistribution of blood flow within an ischemic region of the myocardium occurs with either beta$_1$ or a simultaneous beta$_1$ and beta$_2$ receptor blockade. Furthermore, these data indicate a possible advantage of a new cardioselective beta adrenergic antagonist, bevantolol, in improving ischemic subendocardial blood flow and contractile function.

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The use of beta adrenergic receptor antagonists in the treatment of angina pectoris is well established[1,2]; however, the mechanisms by which these agents reduce myocardial ischemia remain controversial. Although most investigators[3,4] favor the concept that beta receptor antagonists reduce ischemia by decreasing myocardial oxygen demands through negative inotropic and chronotropic actions, an increase in oxygen supply caused by increases in blood flow to ischemic areas may also be an important factor.[4,5] Recent studies[6–8] have shown that beta adrenergic antagonists produce a redistribution of blood flow from subepicardium to subendocardium (increased endocardial/epicardial flow ratio) in nonischemic and acutely ischemic dog hearts. Experiments using conscious dogs[5] have shown that propranolol increased blood flow to areas

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if two specific electrophysiologic mechanisms default simultaneously: First, there must be a complete interruption of A-V conduction. Second, there must be a simultaneous cessation or absence of automaticity within or below the A-V junctional region.

Slowing A-V conduction by verapamil is well documented both experimentally[6–9,10] and clinically.[12,19,20] Verapamil produces its negative dromotropic action within the proximal portion of the A-V junction,[9] expressed as prolongation of the A-H interval in the His bundle electrogram. This locally specific effect on conduction in the A-V node and His bundle region is in accord with the known slow channel blocking properties of verapamil because the slow component of the inward current contributes little to the action potential upstroke recorded from cells of the lower A-V junction and in the normal Purkinje cells of the bundle of His.[21]

Effects of verapamil on A-V node and junction: In the intact dog verapamil selectively injected into the A-V nodal artery readily prolonged the A-H interval, but greater degrees of block required comparatively high concentrations. When third degree A-V block was produced, the escape rhythm each time was of A-V junctional origin. Previous investigations have shown that there are two forms of rhythm that emerge from the A-V junction of the dog (AVJ-1 and AVJ-2).[16,17] Recently, we have reported that the faster of these two A-V junctional rhythms (AVJ-1) is about 10 times less sensitive to the depressant action of verapamil than is the sinus node.[9] The other and slower A-V junctional rhythm (AVJ-2) is normally insensitive to verapamil.[9] In each of the present experiments in which verapamil, selectively perfused into the A-V nodal artery, caused transient third degree A-V block, only AVJ-2 rhythm, sometimes alternating with a slow AVJ-1 rhythm, emerged.

The differential sensitivity of the sinus node and the A-V junctional region to verapamil is well known. Microelectrode studies have shown that concentrations of verapamil that greatly reduced the diastolic potential and the overshoot of transmembrane sinus nodal potentials in isolated rabbit atria did not yet affect A-V node action potentials.[22] Furthermore, concentrations of verapamil that greatly diminished the amplitude of the action potentials in the upper and middle portions of the A-V node of isolated rabbit heart had very little effect on cells of the lower A-V junctional region.[6,18] Our present and previous[9] results are in accord with these microelectrode studies. The entire A-V junctional region must have a greater resistance to verapamil than does the sinus node, and the more distal region of the A-V junctional region must be even more resistant than the more proximal portion.

With those considerations in mind we postulate that verapamil impairs A-V conduction through depression of cells in the upper segment of the A-V junction and that third degree A-V block occurs when most, but not all, of the A-V junction is markedly depressed. Because the effects of verapamil on rhythm of the AVJ-2 type is normally negligible in our experiments, and because the lower A-V junction region is extremely resistant to calcium antagonists,[6,18] we further postulate that the actual site of origin of AVJ-2 rhythm is in the verapamil-*insensitive* portion of the A-V junctional region. This postulate logically implies that severely impaired A-V conduction occurs concomitantly with marked depression of the faster of the two subsidiary A-V junctional rhythms (AVJ-1), and that its site of origin is located in the verapamil *sensitive* portion of the normal A-V junctional area.

Adrenergic influences on effects of verapamil: Whereas the resistance to verapamil is greater in the A-V junction than in the sinus node, the reverse appears to be true with respect to the dependence on adrenergic influences by those two major centers of automaticity. We have previously shown[23] that the A-V junctional region exhibits an impressive dependence on adrenergic neural influences, whereas the same deprivation of adrenergic neural control has much less effect on the sinus node. Similar observations have been made by other investigators.[24] These findings suggest that the resistance to effects of verapamil may be at least partly determined by local variations in the response of certain automatic cells to adrenergic influences. Our study demonstrates that the A-V junction becomes more vulnerable to verapamil when either beta receptors are blocked or local catecholamine stores are depleted. However, concentrations of verapamil that did *not* produce high degree block in the normal preparation were frequently associated with prolonged ventricular standstill after eliminations of adrenergic influences in the A-V junction. This observation not only suggests that the combination of verapamil and absence of adrenergic input to the A-V junction is profoundly more effective, but also demonstrates that the slow A-V junctional rhythm that was not arrested by either adrenergic deprivation alone[23] or verapamil alone[9,18] is readily suppressed by their combination.

Clinical implications: If human cardiac responses in this respect prove to be similar to those in the dog, then due caution should accompany the use of verapamil in patients receiving beta receptor blocking agents.[10–12] Furthermore, because myocardial catecholamine stores are known to be small in patients with congestive heart failure, verapamil must be utilized only with due caution in such patients.

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and in two of these three dogs there was a transient episode of A-V junctional tachycardia. Three to 5 minutes after this injection of norepinephrine the A-V interval again was prolonged, and second degree heart block developed in one dog, whereas first degree block continued in the two other dogs. A second injection of norepinephrine delivered 30 minutes after the first injection caused A-V junctional tachycardia for 1 to 2 minutes in all three dogs. The tachycardia was followed by normal sinus rhythm with a normal A-H interval; this lasted for 30 minutes, when the experiment was terminated.

Discussion

Electrophysiologic effects of verapamil: Selective perfusion of verapamil into the atrioventricular nodal artery when local adrenergic activity is impaired produces prolonged ventricular asystole. This occurs only

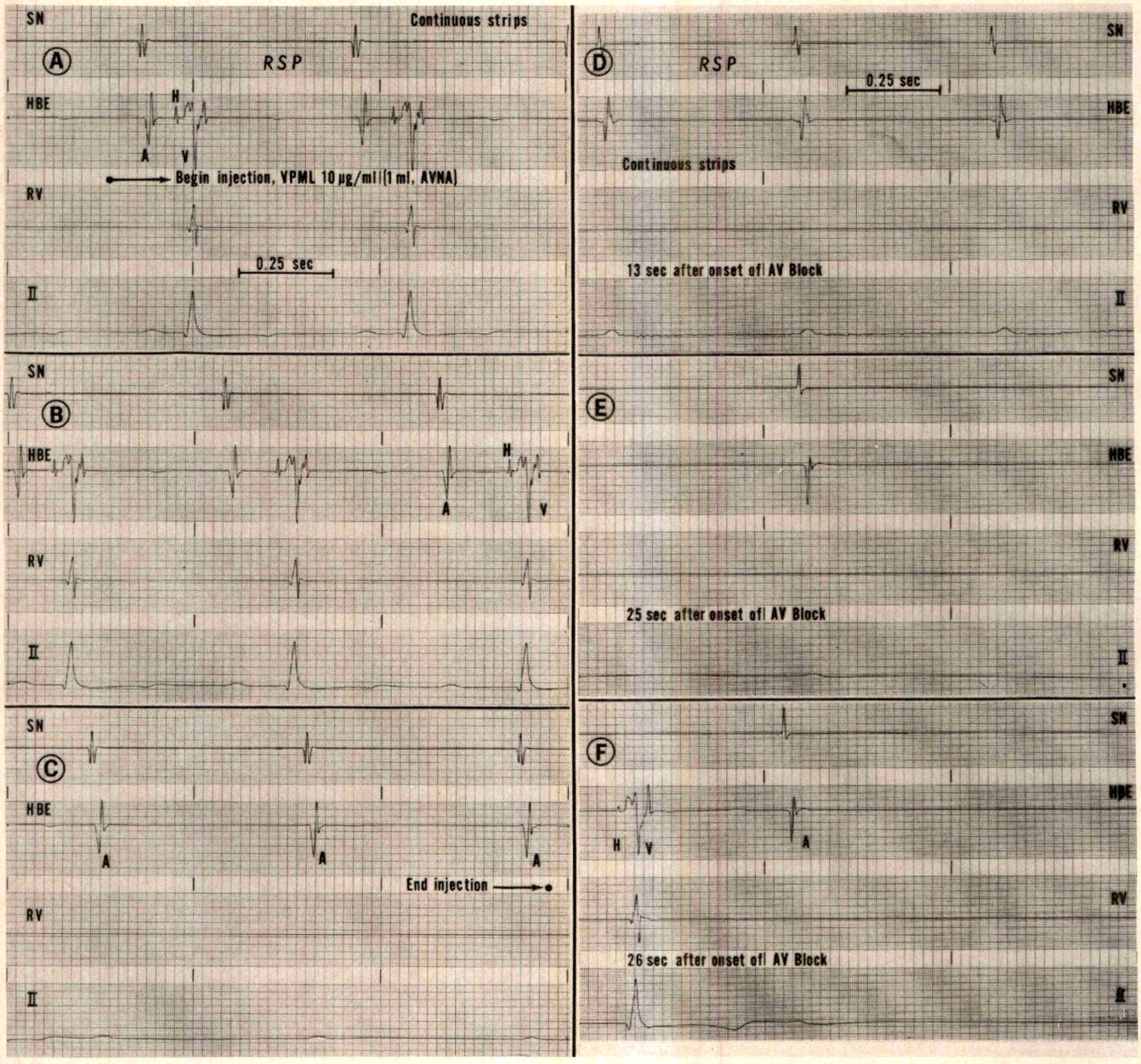

FIGURE 2. Effect of verapamil injected into the atrioventricular (A-V) nodal artery of a dog pretreated with reserpine (RSP) (**Panels A** and **B**). Five beats after the onset of injection third degree A-V block develops (**Panel C**). **Panel D** shows the absence of any ventricular activity as in the previous **Panel C.** However, **Panel E** illustrates a profound sinus slowing that developed rapidly between 20 and 25 seconds after the onset of A-V block. There is still no ventricular electrical activity. **Panel F** illustrates the first escape beat that emerged as late as 26 seconds after the onset of block. This escape beat is also of A-V junctional origin. (See Ref 17 and text for discussion.) AV = atrioventricular.

two other dogs there was a short period of 3:2 alternating with 4:3 A-V block.

Effect of verapamil selectively perfused into the A-V nodal artery of dogs pretreated with reserpine: In 10 such dogs with a control sinus rate of 114 ± 13 beats/min, verapamil, 10 μg/ml, was selectively perfused into the A-V nodal artery (Table II). In each dog third degree A-V block developed within three to six beats. In three dogs the ventricular pause lasted 6, 8 and 9 seconds, respectively, before a slow A-V junctional rhythm emerged at rates of 15 to 30 beats/min. In each of these three dogs A-V block waned to Wenckebach periodicity (3:2 to 4:3 or 5:4), followed by progressive and slow return to 1:1 conduction within 2 hours. In four dogs ventricular asystole lasted from 10 to 20 seconds before a similarly slow A-V junctional rhythm escaped. In the three remaining dogs ventricular asystole lasted 25 to 30 seconds after the selective injection of verapamil into the A-V nodal artery (Fig. 3 and 4). In these three latter dogs norepinephrine, 2 ml, 0.1 μg/ml, was injected into the A-V nodal artery exactly 30 seconds after onset of verapamil-induced ventricular asystole. In each dog A-V conduction was restored within 5 to 10 seconds; 1:1 conduction was observed within 1 minute,

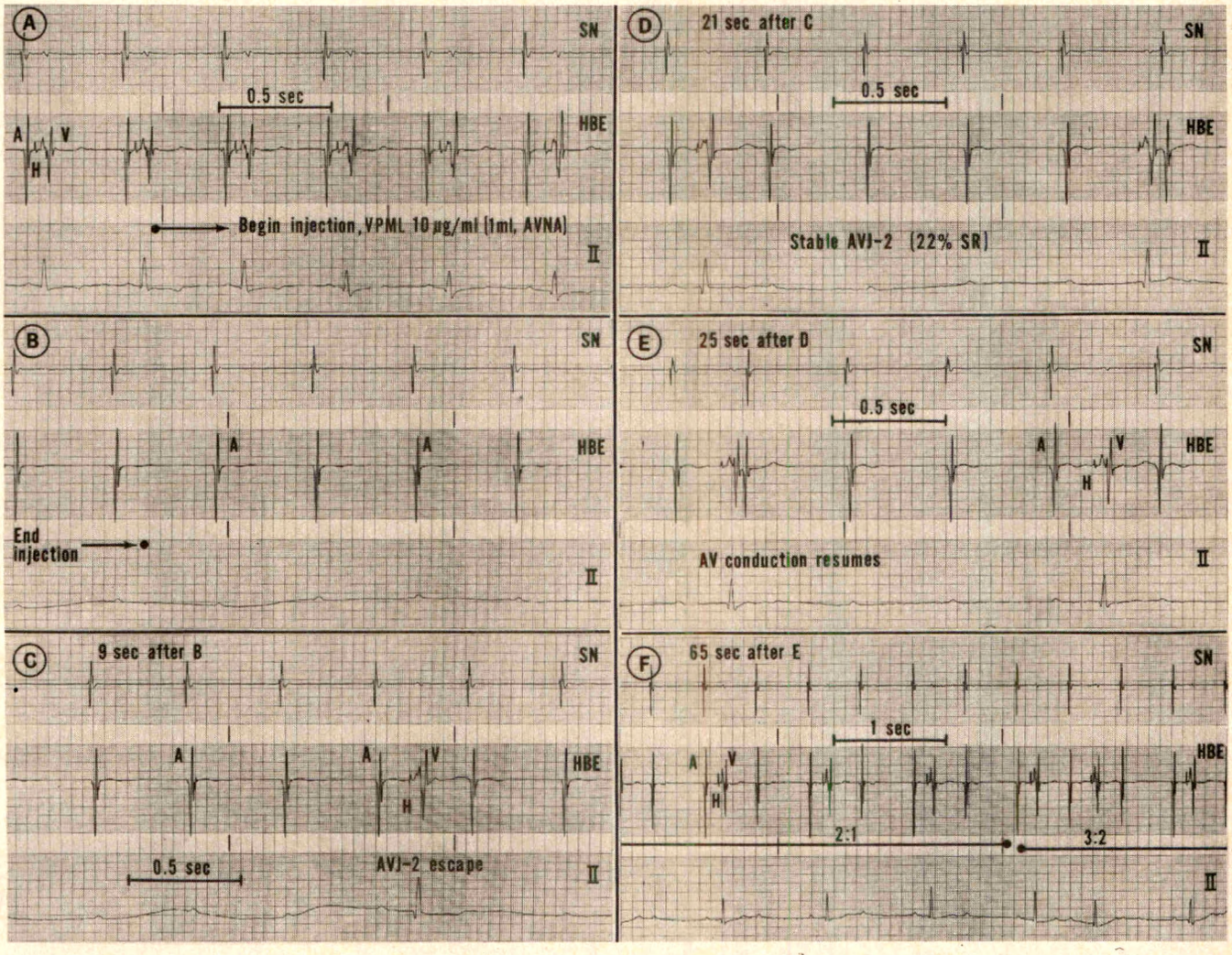

FIGURE 1. Effect of verapamil (VPML) selectively perfused into the atrioventricular nodal artery (AVNA) after beta receptor blockade (propranolol, 10 μg/ml). The **black dots** and **arrows** on **Panels A** and **B** indicate the beginning and completion of the injection. Note the immediate prolongation of the P-R interval and the A-H interval of the His bundle electrogram (HBE) and the rapid progression to third degree A-V block (**Panel B**). **Panel C** shows the first escape beat 12 seconds after the onset of A-V block. This escape beat is of A-V junctional origin (AVJ-2). The QRS complex is narrow and the His deflection precedes the QRS complex. Because of the changed polarity of the His deflection, the narrower H-V interval and the loss of the S wave in surface lead II this A-V junctional escape beat is considered to be an AVJ-2 escape beat. (See Ref 17 and text for discussion.) **Panel D** illustrates the phase of the experiment during which a regular AVJ-2 rhythm drove the ventricles. The rate of this slow but stable A-V junctional rhythm is virtually exactly 22 percent of the sinus nodal rate (SR). **Panel E** illustrates resumption of A-V conduction. Note the change in polarity of the His spike, the lengthening of the H-V interval and the return of an S wave in the surface lead II. **Panel F** demonstrates the progressive recovery of A-V conduction passing through phases of 2:1 and 3:2 A-V block. Recordings in this and the next figure **from top to bottom** represent bipolar electrograms from the vicinity of the sinus node (SN); His bundle electrogram (HBE) with A wave (A), His spike (H) and ventricular complex (V); right ventricular bipolar electrogram (RV); and surface lead II.

adjusted according to a continuous readout of the end tidal carbon dioxide concentration measured with a gas analyzer (Beckman LB-2). The chest was opened in the right fourth intercostal space and the A-V nodal artery was cannulated with a small polyethylene catheter.[13] The entire remaining coronary circulation as well as the normal innervation of the heart was preserved intact.[14] Central aortic pressure was measured with a catheter placed through the right carotid artery and attached to a transducer. Local electrograms were recorded from bipolar electrodes sewn on the right atrium directly adjacent to the sinus node and on the outflow tract of the right ventricular surface, together with a surface lead II or III electrocardiogram. In each dog a His bundle electrogram was obtained with a standard pacing electrode catheter (no. 5F or 6F, 10 mm interpolar distance) introduced through the right or left subclavian artery into the aortic root.[15] A tachogram was derived from the right ventricular electrogram. Injection into the cannulated A-V nodal artery was performed with a hand syringe within 2 to 3 seconds and the total volume injected as 1 ml. Adequacy of A-V junctional perfusion was assessed with acetylcholine chloride, 0.5 μg/ml, injected into the A-V nodal artery. Such injections cause an immediate but transient complete A-V block that lasts 3 to 5 seconds.[16,17]

Protocol: Racemic verapamil hydrochloride (Knoll Pharmaceutical Co.) was diluted in Ringer's solution. The concentrations used were 10 and 25 μg/ml. Other test substances utilized were also prepared in Ringer's solution, and they include racemic propranolol hydrochloride, 10, 20 and 50 μg/ml, and l-norepinephrine bitartrate, 0.1 μg/ml. Catecholamine depletion was achieved with reserpine, 0.5 mg/kg, administered intramuscularly on 2 successive days before the study.

Results

Effect of verapamil selectively perfused into the A-V nodal artery of normal dogs: In five dogs during the stable sinus rhythm of 151 ± 16 beats/min (mean ± standard error of the mean), verapamil was injected selectively into the A-V nodal artery. Injection of 10 μg/ml regularly caused an increase in A-V conduction time, expressed exclusively at the A-H level of the His bundle electrogram (Table I). In three dogs the depressed A-V conduction progressed to 2:1 block, which was transient (15 to 30 seconds), and one of those three dogs had brief episodes of 4:1 block. None had third degree A-V block, and complete recovery to normal A-V conduction occurred within 30 minutes.

In five different dogs with a sinus rate of 146 ± 13 beats/min, verapamil, 25 μg/ml, was the first concentration perfused into the A-V nodal artery (Table I). This caused a rapidly progressing prolongation of the A-H interval, and within 3 to 17 beats transient third degree A-V block developed in three of these five dogs. In the remaining two dogs this injection resulted only in 3:2 and then in 2:1 block. The total duration of third degree A-V block was again brief, not exceeding 3 minutes, and the escape time for an A-V junctional pacemaker to emerge and drive the ventricles ranged from 3 to 6 seconds. Recovery was again steadily progressive. After 20 to 30 minutes, 1:1 conduction resumed and was regularly preceded by Wenckebach periodicity in each dog.

Effect of verapamil selectively perfused into the A-V nodal artery after selective beta blockade of the A-V junction: In two dogs 10 μg/ml of propranolol injected selectively into the A-V nodal artery abolished the A-V junctional tachycardia caused by the injection of norepinephrine, 0.1 μg/ml, by way of the same route. In three other dogs 20 μg/ml of propranolol and in one dog 50 μg/ml of propranolol was required to eliminate this type of A-V junctional tachycardia. After the establishment of selective beta receptor blockade in the A-V junctional region of these six dogs, the sinus rate remained the same as that observed before propranolol and averaged 151 ± 17 beats/min. The P-R interval was prolonged by 10 to 15 msec after propranolol. Verapamil, 10 μg/ml, was then selectively perfused into the A-V nodal artery (Table II), causing a progressive prolongation of the A-H interval that began within a few beats after onset of injection. Four of the six dogs had transient third degree A-V block, whereas two had only partial (2:1 or 4:1) A-V block. The duration of third degree A-V block was from 1 to 4 minutes and the escape time for A-V junctional rhythm was 3, 8, 11 and 12 seconds, respectively (Fig 1 and 2). Sixty minutes after the injection of verapamil (after administration of propranolol) the A-V conduction time had returned to the control level and the response to norepinephrine was indistinguishable from that observed before propranolol. At that time a second selective injection of verapamil, 10 μg/ml, was performed. In four dogs this injection caused only a first degree heart block, but in the

TABLE I

Effect of Verapamil Selectively Perfused Into the A-V Nodal Artery of Normal Dogs

Degree of Block	Verapamil, 10 μg/ml (5 dogs)	Verapamil, 25 μg/ml (5 dogs)
1°	5	5
2°	3	5
3°	0	3
Asystole*	0	0

* Defined as no ventricular activity for at least 10 seconds.

TABLE II

Effect of Verapamil (10 μg/ml) Selectively Perfused Into the A-V Nodal Artery After Beta Receptor Blockade With Propranolol or Pretreatment With Reserpine

Degree of Block	After Propranolol (6 dogs)	After Reserpine (10 dogs)
1°	6	10
2°	6	10
3°	4	10
Asystole	2	7

Experimental Studies on the Pathogenesis of Asystole After Verapamil in the Dog

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The effect of verapamil on automaticity and conduction in the atrioventricular (A-V) junctional region was studied in anesthetized dogs. In five normal dogs verapamil, 10 μg/ml, was selectively perfused into the A-V nodal artery and caused first degree heart block, which progressed to second degree heart block in three of the five. Higher concentrations of verapamil, 25 μg/ml, caused complete heart block in three of five other dogs, but no episodes of asystole (defined as a ventricular pause of 10 or more seconds). In six other dogs after beta receptor blockade with propranolol, 20 μg/ml, perfused into the A-V nodal artery, verapamil, 10 μg/ml, regularly caused second degree heart block; in four of the six dogs there was a transient episode of third degree A-V block, and in two of these there was a period of asystole. In each of the 10 dogs pretreated with reserpine, verapamil, 10 μg/ml, caused third degree A-V block; in seven of these there was a period of asystole with ventricular standstill up to 30 seconds. Concentrations of verapamil that do not produce high grade heart block in the normal heart thus readily cause both high grade block and prolonged ventricular standstill after elimination of adrenergic influences in the A-V junction.

Verapamil is a potent inhibitor of calcium influx across the excited membrane of cardiac and smooth muscle cells.[1–4] As one consequence, the impairment of calcium supply to the contractile system reduces the peak developed force, which in turn decreases adenosine triphosphate (ATP) consumption and myocardial oxygen requirement. Verapamil has also become recognized as an effective antiarrhythmic drug,[5–8] particularly for slowing ventricular rate during supraventricular tachycardia.[5,7] Stimulation of beta adrenergic receptors with catecholamines can minimize or even transiently abolish the negative chronotropic effect of verapamil selectively perfused into the sinus nodal artery.[9] As a clinical corollary, it has been suggested that the asystole that may result from intravenous administration of verapamil is in part due to the synergistic influence of substances having beta receptor blocking actions.[10–12]

In this report we describe our investigations of this purported synergism. Experiments were conducted to examine the related effects of verapamil and propranolol in both automaticity and conduction in the atrioventricular (A-V) junctional area. Experiments were also performed in which verapamil was selectively perfused into the A-V junctional region of hearts previously depleted of their catecholamine stores with reserpine.

Methods

Experimental procedure: Twenty-six mongrel dogs weighing 18 to 22 kg were anesthetized with sodium pentobarbital, 20 to 30 mg/kg body weight, administered intravenously. Ventilation was maintained through a cuffed endotracheal tube by intermittent positive pressure supplying room air at a volume

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(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR)
Inderal® BRAND OF propranolol hydrochloride **A beta-adrenergic blocking agent**

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

ACTIONS: INDERAL is a beta-adrenergic receptor blocking drug, possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available beta receptor sites. When access to beta receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

Propranolol is almost completely absorbed from the gastrointestinal tract, but a portion is immediately bound by the liver. Peak effect occurs in one to one and one-half hours. The biologic half-life is approximately two to three hours. Propranolol is not significantly dialyzable. There is no simple correlation between dose or plasma level and therapeutic effect, and the dose-sensitivity range as observed in clinical practice is wide. The principal reason for this is that sympathetic tone varies widely between individuals. Since there is no reliable test to estimate sympathetic tone or to determine whether total beta blockade has been achieved, proper dosage requires titration.

Beta receptor blockade is useful in conditions in which, because of pathologic or functional changes, sympathetic activity is excessive or inappropriate and detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

The proper objective of beta blockade therapy is to decrease adverse sympathetic stimulation but not to the degree that may impair necessary sympathetic support.

Propranolol exerts its antiarrhythmic effects in concentrations associated with beta-adrenergic blockade and this appears to be its principal antiarrhythmic mechanism of action. The membrane effect also plays a role, particularly, some authorities believe, in digitalis-induced arrhythmias.

Beta-adrenergic blockade is of unique importance in the management of arrhythmias due to increased levels of circulating catecholamines or enhanced sensitivity of the heart to catecholamines (arrhythmias associated with pheochromocytoma, thyrotoxicosis, exercise).

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential and depresses cardiac function.

Propranolol may reduce the oxygen requirement of the heart at any given level of effort by blocking catecholamine-induced increases in heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. On the other hand, propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure, and systolic ejection period.

If the net physiologic effect of beta-adrenergic blockade in angina is advantageous, it would be expected to manifest itself during exercise by delayed onset of pain due to decreased oxygen requirement.

INDICATIONS: Cardiac Arrhythmias: *1.) Supraventricular arrhythmias:* a) Paroxysmal atrial tachycardias, particularly those arrhythmias induced by catecholamines or digitalis or associated with the Wolff-Parkinson-White syndrome. (See W-P-W under WARNINGS.) b) Persistent sinus tachycardia which is noncompensatory and impairs the well-being of the patient. c) Tachycardias and arrhythmias due to thyrotoxicosis when causing distress or increased hazard and when immediate effect is necessary as adjunctive, short term (2-4 weeks) therapy. May be used with, but not in place of, specific therapy. (See Thyrotoxicosis under WARNINGS.) d) Persistent atrial extrasystoles which impair the well-being of the patient and do not respond to conventional measures. e) Atrial flutter and fibrillation when ventricular rate cannot be controlled by digitalis alone, or when digitalis is contraindicated.

2.) Ventricular tachycardias: Ventricular arrhythmias do not respond to propranolol as predictably as do the supraventricular arrhythmias. a) Ventricular tachycardias: With the exception of those induced by catecholamines or digitalis, INDERAL is not the drug of first choice. In critical situations when cardioversion technics or other drugs are not indicated or are not effective, INDERAL may be considered. If, after consideration of the risks involved, INDERAL is used, it should be given intravenously in low dosage and very slowly. (See DOSAGE AND ADMINISTRATION.) *Care in the administration of* INDERAL *with constant electrocardiographic monitoring is essential as the failing heart requires some sympathetic drive for maintenance of myocardial tone.* b) Persistent premature ventricular extrasystoles which do not respond to conventional measures and impair the well-being of the patient.

3.) Tachyarrhythmias of digitalis intoxication: If digitalis-induced tachyarrhythmias persist following discontinuance of digitalis and correction of electrolyte abnormalities, they are usually reversible with *oral* INDERAL. Severe bradycardia may occur. (See OVERDOSAGE OR EXAGGERATED RESPONSE.)

Intravenous propranolol hydrochloride is reserved for life-threatening arrhythmias. Temporary maintenance with oral therapy may be indicated. (See DOSAGE AND ADMINISTRATION.)

4.) Resistant tachyarrhythmias due to excessive catecholamine action during anesthesia. Tachyarrhythmias due to excessive catecholamine action during anesthesia may sometimes arise because of release of endogenous catecholamines or administration of catecholamines. When usual measures fail in such arrhythmias, INDERAL may be given intravenously to abolish them. All general inhalation anesthetics produce some degree of myocardial depression. Therefore, when INDERAL is used to treat arrhythmias during anesthesia, it should be used with extreme caution and constant ECG and central venous pressure monitoring. (See WARNINGS.)

Hypertrophic Subaortic Stenosis: INDERAL is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL also improves exercise performance. The effectiveness of INDERAL in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta receptor stimulation. Clinical improvement may be temporary.

Pheochromocytoma: After primary treatment with an alpha-adrenergic blocking agent has been instituted, INDERAL may be useful as *adjunctive* therapy if the control of tachycardia becomes necessary before or during surgery.

It is hazardous to use INDERAL unless alpha-adrenergic blocking drugs are already in use, since this would predispose to serious blood pressure elevation. Blocking only the peripheral dilator (beta) action of epinephrine leaves its constrictor (alpha) action unopposed.

In the event of hemorrhage or shock, there is a disadvantage in having both beta and alpha blockade since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.

With inoperable or metastatic pheochromocytoma, INDERAL may be useful as an adjunct to the management of symptoms due to excessive beta receptor stimulation.

CONTRAINDICATIONS: INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS: CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (i.e., that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by INDERAL's negative inotropic effect. The effects of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, INDERAL therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.*, isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose.

PRECAUTIONS: Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS: *Cardiovascular:* bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory: bronchospasm

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DOSAGE AND ADMINISTRATION: The dosage range for INDERAL is different for each indication.

ORAL

ARRHYTHMIAS—10-30 mg three or four times daily, before meals and at bedtime.

HYPERTROPHIC SUBAORTIC STENOSIS—20-40 mg three or four times daily, before meals and at bedtime.

PHEOCHROMOCYTOMA—*Preoperatively*—60 mg daily in divided doses for three days prior to surgery, concomitantly with an alpha-adrenergic blocking agent.—*Management of inoperable tumor*—30 mg daily in divided doses.

PEDIATRIC DOSAGE At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

INTRAVENOUS Intravenous administration is reserved for life-threatening arrhythmias or those occurring under anesthesia. The usual dose is from 1 to 3 mg administered under careful monitoring, *e.g.* electrocardiographic, central venous pressure. The rate of administration should not exceed 1 mg (1 ml) per minute to diminish the possibility of lowering blood pressure and causing cardiac standstill. Sufficient time should be allowed for the drug to reach the site of action even when a slow circulation is present. If necessary, a second dose may be given after two minutes. Thereafter, additional drug should not be given in less than four hours. Additional INDERAL should not be given when the desired alteration in rate and/or rhythm is achieved.

Transference to oral therapy should be made as soon as possible.

The intravenous administration of INDERAL has not been evaluated adequately in the management of hypertensive emergencies.

OVERDOSAGE OR EXAGGERATED RESPONSE: IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg); IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY.

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS.

HYPOTENSION—VASOPRESSORS, *e.g.* LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE.)

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE.

HOW SUPPLIED: INDERAL (propranolol hydrochloride)

TABLETS: *No. 461*—Each scored tablet contains 10 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100. *No. 462*—Each scored tablet contains 20 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100. *No. 464*—Each scored tablet contains 40 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100. *No. 468*—Each scored tablet contains 80 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

INJECTABLE: *No. 3265*—Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as: 1 ml ampuls in boxes of 10.

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INDERAL®
(PROPRANOLOL HCl)
BETTER SOONER THAN LATER

ALONE Excessive exertions. Emotional upheavals. Anxieties. Stress. Catecholamines rise—atrial pacemakers overrespond.
And the ECG reads PAT. Or persistent sinus tachycardia. Or persistent atrial extrasystoles. Consider INDERAL (propranolol HCl) alone.
When conventional measures fail, a low 10 to 30 mg dose, given t.i.d. or q.i.d., will block cardiac beta-receptors from excessive catecholamine stimulation. Suppress ectopic pacemakers. And permit resumption of normal sinus rhythm. Even when normal sinus rhythm has not been restored, INDERAL slows conduction in the AV node and prolongs its refractory time. Slowed AV conduction will often block reentry circuits, to help restore sinus rhythm.

WITH The ECG reads atrial flutter. Or atrial fibrillation. You have digitalized your patient, but the arrhythmia is not yet controlled. Consider adding INDERAL (propranolol HCl). Combined with digitalis, it obviates increasing digitalis dosage to toxic levels—while slowing the ventricular rate sufficiently to achieve control. INDERAL also complements the action of other agents. Combined with quinidine, it allows lower doses of quinidine—reducing the need for toxic levels. And often, with INDERAL added, atrial arrhythmias respond when no single agent works alone.

INSTEAD The arrhythmia is induced by an antiarrhythmic drug such as digitalis or quinidine. Persists after discontinuance of the drug and correction of electrolyte imbalance. Consider INDERAL instead. Often the drug of choice, except in the presence of serious congestive heart failure. Often, too, INDERAL (propranolol HCl) abolishes supraventricular arrhythmias when either digitalis or quinidine has failed.

With proper patient selection—in the absence of contraindications such as bradycardia, greater than first degree heart block, asthma, and congestive heart failure unless failure is secondary to tachyarrhythmias treatable with INDERAL—serious cardiovascular and respiratory side effects are seldom encountered.*
Rely on it: INDERAL. Alone. With. Or Instead.

*Please turn the page for brief summary of prescribing information on contraindications, adverse reactions, and warnings, including avoidance of abrupt withdrawal.

A PRIME CONSIDERATION FOR SUPRAVENTRICULAR ARRHYTHMIAS

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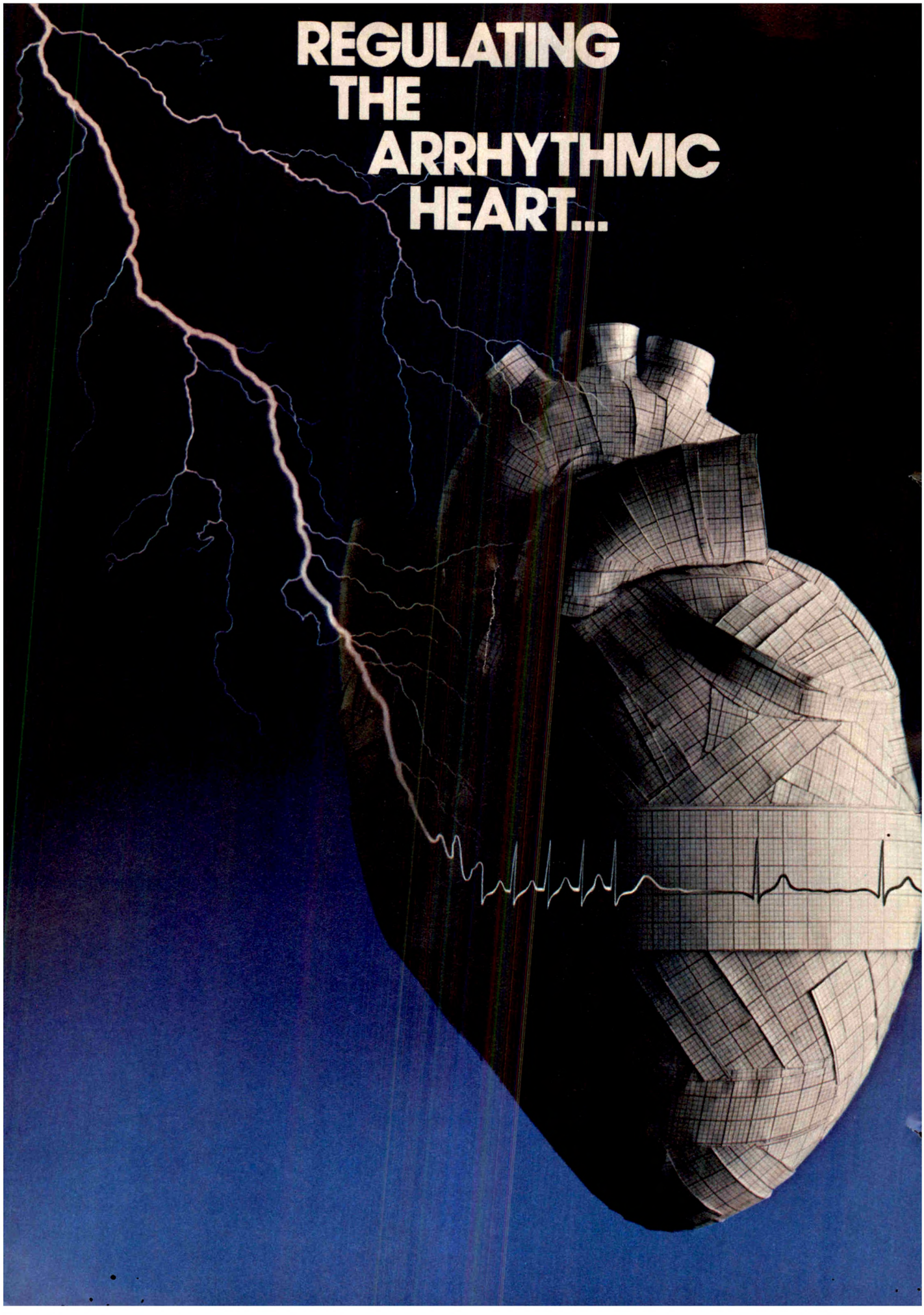
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complexes that differed in configuration from those of sinus beats, (2) heart rate greater than 120/min, (3) no premature P wave preceding the onset of tachycardia and (4) one of the following findings: A-V dissociation, a fusion complex, a capture complex or an isolated premature ventricular complex in the same lead having a similar QRS configuration as that of ventricular tachycardia.

In addition, care was taken to exclude accelerated idioventricular rhythm. Therefore, we excluded any ventricular tachycardia initiated (1) by a ventricular escape complex or (2) by a fusion complex or end-diastolic premature complex with a pattern of sinus rate slowing *preceding* the appearance of ectopic beats.

A bolus injection of lidocaine was administered intravenously in a dose of 50 to 100 mg followed by a 2 to 4 mg/min infusion to patients with any one of the following: (1) bigeminal premature ventricular complexes, (2) multiform premature ventricular complexes, or (3) ventricular tachycardia (with precordial direct current countershock if required).

Electrocardiographic analysis: *This was performed as follows:* (1) measurement of the coupling interval (R-R′) that represented the duration from the preceding R wave of the sinus beat to the R wave of the premature ventricular complex (R′) initiating the tachycardia; (2) measurement of the Q-T interval of the basic sinus rhythm; (3) determination of the prematurity index (R-R′/Q-T) with a value less than 1, considered to be equivalent to the R on T phenomenon, (4) the rate and cycle length of the basic sinus rhythm, and (5) the relation of the premature ventricular complex to the antecedent T wave and onset of the next sinus P wave. The age and sex of the patients, and administration of propranolol, digoxin, procainamide, quinidine and lidocaine were tabulated.

Results

Ventricular tachycardia or fibrillation: Of the 225 patients with acute myocardial infarction, 54 had primary ventricular tachycardia or ventricular fibrillation, or both, fulfilling the criteria of the study. Five of these 54 patients had ventricular fibrillation without ventricular tachycardia and 49 had ventricular tachycardia. In 3 of the 49 patients with ventricular tachycardia ventricular fibrillation developed. The interval between the patients' entry into the unit and the occurrence of ventricular tachyarrhythmia ranged from 18 minutes to 44 hours (mean of 20 ± 7 hours).

Clinical features of patients: There were 34 men and 20 women whose ages ranged from 42 to 81 years (mean age 59 years). At the time of admission, digoxin and propranolol were being taken by 3 patients, propranolol alone by 14 patients and quinidine by 1 patient. The mean (± 1 standard deviation) daily dose of propranolol in the 17 subjects taking the drug at the time of admission was 96 ± 80 mg. Twenty-four hours after admission the propranolol dosage was 70 ± 43 mg. The basic sinus rate for the entire study group was 82 ± 17 beats/min at the time of ventricular tachycardia, whereas the average rate for 13 patients taking propranolol was 72 ± 13. The bases for administration of propranolol before admission to the unit were hypertension (4 patients), angina pectoris (10 patients) and a history of atrial tachyarrhythmia (3 patients). Two patients had a history of prior myocardial infarction. Fifteen patients were receiving intravenous lidocaine by infusion when ventricular tachycardia developed.

Of the 49 patients with ventricular tachycardia 6 had one episode, 11 had two episodes and 32 had three or more episodes, constituting a total 212 occurrences. The mean rate of tachycardia for these episodes was 163 ± 21 beats/min. One hundred sixty-five episodes (78 percent) consisted of three or four ventricular complexes, and 47 (22 percent) consisted of five or more ventricular complexes. There were three episodes of sustained ventricular tachycardia lasting more than 10 minutes; all responded to direct current electrocardioversion. Only one episode of ventricular tachycardia degenerated into ventricular fibrillation.

Coupling (R-R′) intervals in ventricular tachycardia: The coupling intervals of premature depolarizations initiating ventricular tachycardia ranged from 0.26 to 1.04 seconds with a mean of 0.54 ± 0.15 second (Table I). The prematurity index (R-R′/Q-T) of initiating premature complexes ranged from 0.64 to 2.14 with a mean of 1.27 ± 0.31 (Table II). The distribution of coupling intervals for premature ventricular complexes initiating ventricular tachycardia in the 17 patients taking propranolol ranged from 0.27 to 0.84 with a mean of 0.52 ± 0.14 second. Prematurity indexes for the group taking propranolol ranged from 0.76 to 1.94 (mean 1.24 ± 0.25). The prematurity index was less than 0.85 in 17 episodes (8 percent) and less than 1 (R on T) in 42 episodes (20 percent). Interestingly, the initiating complexes of ventricular tachycardia occurred immediately after the onset of a sinus P wave (R on P) in 93 episodes (44 percent) (Fig. 1 and 2). There were 51 episodes of ventricular tachycardia in the group taking propranolol; 20 of these (39 percent) were initiated by the R on P phenomenon. The prevalence of sinus rates

TABLE I

Distribution of Coupling Interval (R-R′) of Premature Complexes Initiating Ventricular Tachycardia and Duration of the Tachycardia

Coupling Interval (second)	Duration of Ventricular Tachycardia				
		>5 QRS Complexes			
	3 to 4 QRS Complexes	<1 Minute	1 to 10 Minutes	>10 Minutes	Total Episodes
≤0.40	33	6	6	2	47
0.41–0.60	85	18	6	1	110
0.61–0.80	41	7	0	0	48
>0.80	6	1	0	0	7
Total episodes	165	32	12	3	212

TABLE II

Distribution of Prematurity Index (R-R′/Q-T) of the Premature Ventricular Complexes Initiating Ventricular Tachycardia and Duration of the Tachycardia

Prematurity Index	Duration of Ventricular Tachycardia				
	3 to 4 QRS Complexes	>5 QRS Complexes			Total Episodes
		<1 Minute	1 to 10 Minutes	>10 Minutes	
<0.85	11	3	2	1	17
0.85–0.99	19	3	2	1	25
1.00–1.19	37	6	3	1	47
1.20–1.39	44	10	3	0	57
1.40–1.59	27	5	2	0	34
1.60–1.79	16	3	0	0	19
1.80–1.99	7	2	0	0	9
≥ 2.00	4	0	0	0	4
Total episodes	165	32	12	3	212

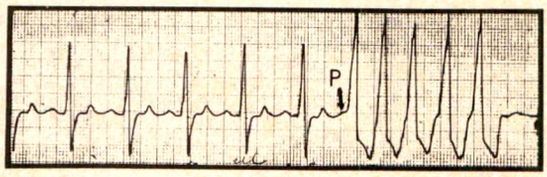

FIGURE 1. Example of R on P phenomenon. Modified lead II of the electrocardiogram demonstrates sinus rhythm and a burst of ventricular tachycardia that is initiated by a premature ventricular complex recorded immediately after inscription of the sinus P wave.

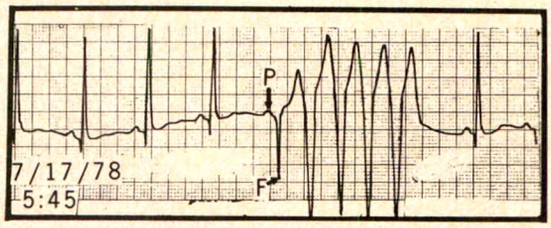

FIGURE 2. Paroxysm of ventricular tachycardia (lead II) initiated by a ventricular fusion complex (F) that occurs immediately after the sinus P wave.

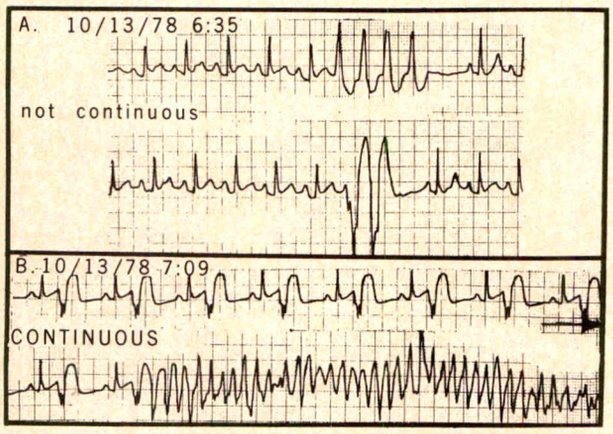

FIGURE 3. Ventricular tachycardia and fibrillation (modified lead II). **A,** ventricular tachycardia with four QRS complexes. The coupling interval of the initiating beat is 0.34 second and the prematurity index is 1.06. **B,** 34 minutes later, ventricular fibrillation follows ventricular bigeminy. The coupling interval of the latter is 0.24 second, and an R on T phenomenon initiates ventricular tachyarrhythmia.

faster than 100/min or slower than 60/min did not differ between subjects who did and did not manifest the R on P phenomenon (Table III). Table IV summarizes the distribution of basic sinus rates in relation to the duration of ventricular tachycardia.

To determine whether there was any correlation between the coupling interval of the initiating premature QRS complex, prematurity index of the initiating ventricular extrasystole or sinus rate with the rate of ventricular tachycardia, these measurements were subjected to statistical analysis. Correlation coefficients for the 212 episodes of ventricular tachycardia were as follows: coupling interval, $r = 0.02$; prematurity index, $r = 0.10$ and sinus rate, $r = -0.01$.

Ventricular fibrillation: Eight patients had primary ventricular fibrillation. In one subject ventricular fibrillation developed after a short paroxysm of ventricular tachycardia (Fig. 3). In the other seven the episodes were initiated by a premature ventricular complex. The coupling intervals of those initiating complexes were 0.24, 0.26, 0.30, 0.34, 0.40, 0.42 and 0.45 seconds, respectively. The prematurity index was less than 1 in four instances and greater than 1 on three occasions. Two of the seven patients had episodes of ventricular tachycardia before the development of ventricular fibrillation.

Discussion

In 1940 Wiggers[8] introduced the concept of ventricular vulnerability and proposed that stimuli introduced

TABLE III

Distribution of Sinus Rates for Subjects With and Without the R on P Phenomenon

Basic Sinus Rate	Episodes of Ventricular Tachycardia	
	Without R on P	With R on P
Sinus tachycardia (>100/min)	16 (13.4%)	12 (12.9%)
Sinus rhythm (60–100/min)	94 (79.0%)	73 (78.5%)
Sinus bradycardia (<60/min)	9 (7.6%)	8 (8.6%)
Total	119 (100%)	93 (100%)

TABLE IV

Distribution of Basic Sinus Rates in Relation to the Duration of Ventricular Tachycardia

Basic Sinus Rate	Duration of Ventricular Tachycardia				
	3 to 4 QRS Complexes	>5 QRS Complexes			Total Episodes
		<1 Minute	1 to 10 Minutes	>10 Minutes	
Sinus tachycardia (>100/min)	19	4	4	1	28
Sinus rhythm					
80 to 100/min	61	11	5	2	79
60 to 79/min	70	15	3	0	88
Sinus bradycardia (<60/min)	15	2	0	0	17
Total episodes	165	32	12	3	212

during late systole might initiate ventricular fibrillation when there were cardiac elements in different stages of refractoriness. Subsequently, Smirk and Palmer[1,2] characterized the hazard of an R wave interrupting an antecedent T wave. The emphasis on this R on T phenomenon was then extended to the management of ischemic heart disease,[3,4] thereby providing a rationale for aggressive therapy of early ventricular depolarizations. The fact that experimental ventricular fibrillation was initiated by early coupling of premature ventricular beats or electric stimuli[5,9] provided a further impetus for the R on T concept. Despite these considerations, studies in experimental animals and human subjects accumulated during the past decade have indicated that ventricular tachyarrhythmias frequently arise in association with late coupled ectopic beats.[10,11] Indeed, the significance of the R on T phenomenon as a harbinger for ventricular tachycardia and fibrillation in clinical settings has been questioned.

Incidence of R on T phenomenon initiating ventricular tachyarrhythmia: Table V summarizes the variability of this association in large numbers of subjects. Dhurandhar et al.[12] reported an R on T complex initiating primary ventricular fibrillation in 16 of 20 patients with degeneration of tachycardia to fibrillation in the other 4 subjects. Lie et al.[13] demonstrated a prematurity index of less than 0.85 in 9 of 20 patients with primary ventricular fibrillation; 7 subjects had an index of 0.85 or greater and the other 4 manifested fibrillation as a progression from tachycardia. El-Sherif et al.[14] found 17 of 20 subjects with primary ventricular fibrillation who had initiating premature ventricular complexes; in 10 of these 17 the prematurity index was less than 1. Chou and Wenzke[15] reviewed conventional electrocardiograms, bedside monitor tracings and Holter recordings from a group of patients with various forms of heart disease. Their data disclosed that relatively late ventricular depolarizations were responsible for the onset of ventricular tachycardia in the majority of instances. Boudoulas et al.[16] reported the more frequent association of both ventricular tachycardia and fibrillation with late onset of premature complexes when compared with the R on T phenomenon. The latter authors coined the term R on R to describe this late onset phenomenon in subjects with ventricular tachyarrhythmias revealed in ambulatory and treadmill stress test electrocardiograms.

Our results indicate that only 42 of 212 episodes (22 percent) of primary ventricular tachycardia occurring in the setting of acute myocardial infarction are presaged by a prematurity index of less than 1 (R on T). Especially noteworthy was the relatively high incidence rate (44 percent, 93 of 212) of ventricular tachycardia in association with a premature QRS complex immediately after the sinus P wave (R on P). The occurrence of this R on P relation over a wide range of sinus rates (Table III) precludes the P-P cycle length as the sole determinant for its occurrence. Additionally, there was no difference in the prevalence of sinus tachycardia or bradycardia in groups with and without the R on P phenomenon.

Among our 54 patients with primary ventricular tachycardia or ventricular fibrillation, or both, fulfilling criteria for entry into this study, 17 (32 percent) were taking propranolol. This finding indicates that a significant number of subjects were receiving a medication

TABLE V

Incidence of R on T Initiating Ventricular Fibrillation (VF) or Ventricular Tachycardia (VT) in Four Reported Series

	VF (no.)	VT (no.)	R on T (no.)	Criteria for R on T	Study Group
Dhurandhar et al.[12]	20	. . .	16	Not indicated	851 patients with acute myocardial infarction
Lie et al.[13]	20	. . .	9	R-R′/RT′ <0.85	262 patients with acute myocardial infarction
El-Sherif et al.[14]	20	. . .	10	R-R′/RT <1	450 patients with acute myocardial infarction
Chou et al.[15]	. . .	44	6	R-R′/RT <1	Hospitalized and ambulatory patients with various types of heart disease

no. = number of patients.

with recognized electrophysiologic properties at the time of admission and the agent may have influenced the occurrence of premature complexes very late in the basic cardiac cycle.

Genesis of ventricular tachycardia: Premature ventricular complexes generated during acute myocardial infarction are generally assumed to result from enhanced automaticity or reentry in the His-Purkinje system.[17] It has been demonstrated that acute coronary occlusion may evoke delayed and sustained myocardial activation at localized sites that will function as a source of reentrant activity with associated premature complexes.[18] Episodes of ventricular tachycardia leading to fibrillation manifest a progressive increase in the ventricular activation time of the successive beats, whereas in self-terminating episodes ventricular activation times progressively decrease.[10] Wellens et al.[19] demonstrated that sustained ventricular tachycardia was rare and possibly due to enhanced automaticity in the setting of acute myocardial infarction. Furthermore, those episodes that did not terminate quickly or become sustained had a propensity for evolving into fibrillation. These latter events were possibly related to reentry in the border zone between infarcted tissue and normal myocardium.[19] For reentry to occur, the time relation between conduction velocity of the excitatory wave and the duration of refractoriness within components of the reentry pathway is critical. It seems logical to assume that in both the infarcted area and in the border zone conditions are constantly changing during the course of acute myocardial infarction.[19] We have demonstrated that 44 percent of ventricular tachycardias occurring during acute myocardial infarction are associated with an R on P phenomenon. The explanation for this strikingly high incidence rate remains conjectural. Atrial contraction attendant on the P wave may have resulted in enhanced left ventricular stretch and alteration of the border zone so that local reentry ensued. Alternatively, the effects imposed by atrial depolarization may have engendered a state that was favorable to arrhythmia.

The mechanical effects of such hemodynamic forces on the genesis of ventricular arrhythmias are currently unclear. They were recently discussed by Goldberg,[20] who noted that some premature ventricular complexes occur at that portion of the cardiac cycle when rapid ventricular filling occurs. If a rapid filling and presystolic clustering of ventricular irritability can be demonstrated in a larger series of subjects with ectopic complexes, the influence of blood impacting on the left ventricular myocardium and its relation to arrhythmias may be elucidated. Because only three subjects had simultaneous ventricular tachycardia and atrial fibrillation no definite conclusion can be determined with regard to this setting. However, it would be important to determine the prevalence of late cycle ventricular tachycardia in a large series of patients with concomitant atrial fibrillation.

Possible mechanisms relating to prematurity and frequency of the ventricular depolarizations: These include the following:

1. *Geometry of the myocardial infarction.* There is experimental evidence indicating a clear correlation between the incidence of ventricular premature complexes and size of infarction as determined by hourly measurements of serum creatine kinase levels in patients[21] and at necropsy in animal preparations.[22]

2. *Very slow reentrant pathways.* Boineau and Cox[18] recorded bipolar left ventricular potentials in dogs subjected to coronary occlusion. They noted sustained desynchronized activity confined to local myocardial areas up to 215 msec after the onset of ventricular activation. These local areas of sustained excitation functioned as a source of reentrant activity and were associated with premature ventricular complexes. Williams et al.[10] performed similar experiments and observed ventricular tachycardia on repeated occasions after ectopic complexes with late diastolic coupling. At any given degree of delay, early depolarizations exhibited more dispersion than those falling later in the cycle. However, they pointed out that late diastolic complexes could become dangerous by inducing fibrillation when the underlying dispersion of ventricular activation was great. Such is the case in the setting of acute myocardial infarction.

3. *Parasystole.* The possible importance of parasystolic foci in initiating premature ventricular complexes late in the cycle must be considered. Using closed loops of ventricular conduction system in canine or bovine hearts, Wit et al.[23] demonstrated many possible mechanisms for ventricular tachycardia. Excitation reciprocating between a pair of foci, each capable of yielding return extrasystoles along with a single or persistent circus movement, were postulated as reasonable explanations for the activity of parasystolic foci and ventricular tachycardias. Alternatively, a parasystolic focus with early periods of exit block may provide an explanation for late cycle tachycardias.[24] Dependence of the onset and frequency of ventricular tachycardia on the degree of exit block and delay in conduction between the ectopic focus and surrounding myocardium has been invoked to account for late cycle slow or rapid rates in subjects with acute myocardial infarction.[25]

4. *Afterpotentials.* The emergence of afterpotentials may precipitate ventricular arrhythmia late in the cardiac cycle. An early afterhyperpolarization need not terminate in a return to the membrane potential prevailing before the action potential but may instead lead directly into a delayed afterdepolarization. A single driven action potential may thus give rise to a burst of extrasystoles. Activation of the ventricle may not occur until the triggered impulse has traveled from its site of origin into the muscular mass, and the time needed for such depolarization could be long if the focus were isolated and connected to the ventricular mass only by a slowly conducting pathway.[26]

5. *Propranolol.* Kupersmith et al.[27] studied the electrophysiologic and antiarrhythmic effects of propranolol in canine acute myocardial ischemia. This drug slowed conduction in the ischemic zone yet reduced the disparity in action potential duration between ischemic and normal zones. It is unlikely that the propranolol administered in 17 of our patients was the sole reason for late diastolic ventricular ectopic complexes. The

coupling intervals, prematurity indexes and incidence of R on P phenomenon initiating ventricular tachycardia appeared to approximate those determined for subjects not taking this medication.

Role of atrial depolarization on ventricular activation: In those seven patients with ventricular fibrillation initiated by a premature ventricular complex, none of the initiating complexes occurred directly after the onset of a sinus P wave. It is possible that presystolic left atrial activity does not result in a progressive increase of the localized ventricular activation time of successive complexes. If such is the case, the R on P phenomenon would not result in ventricular fibrillation. The effect of atrial depolarization or contraction on the reentry pathway between infarcted area and normal myocardium and the localized ventricular activation time appears to be a subject that warrants further investigation.

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Epicardial Activation in Human Left Anterior Fascicular Block

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Four patients with coronary artery disease and chronic marked left axis deviation, defined as a frontal QRS axis more negative than −45°, were studied with epicardial mapping during coronary bypass surgery. All patients had normal right ventricular and inferior left ventricular epicardial breakthrough sites and activation sequence. Normal breakthrough in the basal anterolateral left ventricular epicardium was absent in all four patients. Two patients had breakthrough in the apical region of the anterolateral left ventricle. In the other two this region was activated from wave fronts emerging in the right ventricle and inferior left ventricle. The latest site of left ventricular activation was the basal segment of the anterolateral wall, a site never found to be the latest activated in our previously studied patients without conduction defects. This site was activated during or slightly after the terminal portion of the QRS complex. It is concluded that marked left axis deviation in patients with coronary artery disease reflects delayed activation of the basal anterolateral left ventricle, and is consistent with the presence of block or delay in the anterior "fascicle" of the left bundle branch.

The criteria for diagnosis of specific intraventricular conduction defects in human beings have largely been derived from serial electrocardiographic observations in patients and analysis of conduction defects produced during animal experimentation. In contrast, the electrocardiographic criteria for diagnosis of anatomic abnormalities, such as hypertrophy or infarction, are subject to postmortem verification.

The criteria for diagnosis of left anterior fascicular block were derived from serial electrocardiographic observations[1–4] and knowledge of the structure of the conduction system[5] and results of surgical section of the anterior division of the left bundle branch in animals.[6–12] In patients with diagnosed left anterior fascicular block, although pathologic studies frequently reveal lesions in the left bundle branch system,[13–19] it is impossible for the pathologist to determine whether diseased portions of the His-Purkinje system were able to conduct during life.[19] Thus, the diagnosis of left anterior fascicular block is not subject to absolute pathologic confirmation.

Another approach to the examination of the electrocardiographic diagnosis of left anterior fascicular block would be to evaluate the pattern of ventricular activation revealed by cardiac mapping in patients with this electrocardiographic abnormality. In this study, we examined the pattern of epicardial activation in patients with electrocardiographically diagnosed left anterior fascicular block in an attempt to understand further this intraventricular conduction defect. The epicardial maps obtained were consistent with conduction delay localized to the anterolateral left ventricle.

Methods

Patient selection: Four patients with electrocardiographic left anterior fascicular block undergoing open heart surgery were studied. The criteria for

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inclusion in the study were: (1) left anterior fascicular block on preoperative electrocardiogram as defined by a QRS duration of less than 0.12 second, a negative mean frontal plane QRS axis of −45° or more and a qR complex in lead I and an rS complex in leads II and III[4]; (2) absence of previous myocardial infarction as judged from the electrocardiogram and left ventriculogram (no wall motion abnormality); (3) absence of left or right ventricular hypertrophy by precordial lead voltage criteria; (4) indications for elective cardiac surgery (angina pectoris in all cases); and (5) the signing of preoperative informed consent for epicardial mapping, under a protocol approved by the Human Investigation Committee of the University of Illinois.

Epicardial mapping: Epicardial mapping was performed before initiation of cardiopulmonary bypass using previously described techniques.[20,21] Three of seven continuously monitored electrocardiographic leads (I, II, III, aVR, aVL, aVF and V_6) were displayed simultaneously with a bipolar right ventricular reference electrogram and two bipolar electrograms from the exploring probe, on an Electronics for Medicine recorder (model VR-6 or DR-8, Minneapolis, Minnesota). Recordings were made at 100 and 200 or 250 mm/sec. The timing of local electrograms, in milliseconds, reflected the mean of 5 to 10 beats measured during stable sinus rhythm, from the onset of the earliest QRS deflection in multiple surface or reference leads to the point at which the first high frequency deflection crossed the baseline in the local electrogram. In all, 54 to 75 points were mapped on the epicardial surface of each heart, without displacement of the heart, utilizing landmarks as previously detailed.[21] Stability of the map was ensured by noting (1) a stable sinus rhythm throughout monitoring, with sinus rate varying by no more than 10 beats/min, and (2) a stable QRS configuration during monitoring.

The 12 lead postoperative electrocardiogram resembled the preoperative, in regard to QRS duration, configuration and axis. No morbidity was encountered from the mapping procedure.

Definitions: Epicardial breakthrough was defined as the site of emergence of a radially propagating wave front at the epicardial surface, producing an island of early activation, completely surrounded by points of later activation. The site of latest epicardial activation was noted for the ventricles as a whole and was considered the site of latest recordable ventricular activation. The site of latest activation was also noted for each ventricle.

Comparison with epicardial maps in patients with normal QRS complex: In an attempt to delineate the abnormalities associated with left anterior fascicular block, we compared the epicardial maps obtained in this study with patterns of activation seen in patients without intraventricular conduction defects. These data in 11 patients with a normal QRS complex were recently reported by our laboratory.[21]

For comparison purposes, the following features were noted for epicardial mapping data in all patients without conduction defects[21]: (1) Earliest epicardial breakthrough in the anterior paraseptal right ventricle, 7 to 25 (mean 17) msec after onset of the QRS complex. (2) Two to four subsequent epicardial breakthroughs in all patients, at multiple sites in the inferior right ventricle, inferior left ventricle and the anterolateral left ventricle. Anterolateral left ventricular breakthrough was almost always present near the base of the left ventricle, and often at sites near the apex. (3) Latest epicardial activation contiguous to the atrioventricular (A-V) groove, at any site on the basal right or left ventricles except the anterolateral left ventricle. The timing of this latest epicardial activity occurred 63 to 96 (mean 77) msec after the onset of the QRS complex, and within 20 msec of the end of the QRS complex in all patients.

Results

Clinical data (Table I): The study group consisted of one woman and three men, aged 48 and 54, 52 and 43 years, respectively. Their preoperative electrocardiograms are shown in Figure 1. The QRS duration ranged from 80 to 110 (mean 100) msec and the frontal plane QRS axis from −45° to −60° (mean −49°). All patients had a qR complex in lead I and an rS complex in leads II and III. Electrocardiographic criteria for myocardial infarction were not present in any patient, although three patients (Cases 1 to 3) gave a history of a previous heart attack, of unknown anatomic location. Left ventriculography revealed moderate generalized hypokinesia in one patient (Case 2) but a normal contractile pattern in the other three patients.

Typical epicardial map (Fig. 2): The four epicardial maps obtained in this study were all similar (see later). A typical example (from Patient 1) is shown in Figure 2. The local activation times in milliseconds are shown

TABLE I

Clinical and Epicardial Data

Case no.	Age (yr) & Sex	QRS Duration (msec)*	QRS Axis (°)	Epicardial Breakthrough Site and Timing (msec)						Latest Epicardial Activation Site and Timing (msec)	
				RV			LV				
				BT_1	BT_2	BT_3	BT_1	BT_2	BT_3	RV	LV
1	48F	110	−45	ARV 19	—	—	ILV 19	AALV 47	—	RVOT 77	BALV 125
2	54M	110	−45	ARV 20	IRV 34	IRV 35	ILV 29	ILV 37	—	RVOT 81	BALV 124
3	52M	80	−60	ARV 28	IRV 29	—	ILV 45	ILV 50	—	ARV 80	BALV 70
4	43M	100	−45	ARV 20	IRV 37	—	ILV 25	ILV 28	AALV 38	IRV 88	BALV 68
Mean	49	100	−49	22	34	35	30	41	38	82	97

* Epicardial events are timed (msec) from onset of the QRS complex.

AALV = apical anterolateral left ventricle; ARV = anterior right ventricle; BALV = basal anterolateral left ventricle; B_1, B_2 and B_3 = first, second and third epicardial breakthroughs, respectively; ILV = inferior left ventricle; IRV = inferior right ventricle; LV = left ventricle; RV = right ventricle; RVOT = right ventricular outflow tract.

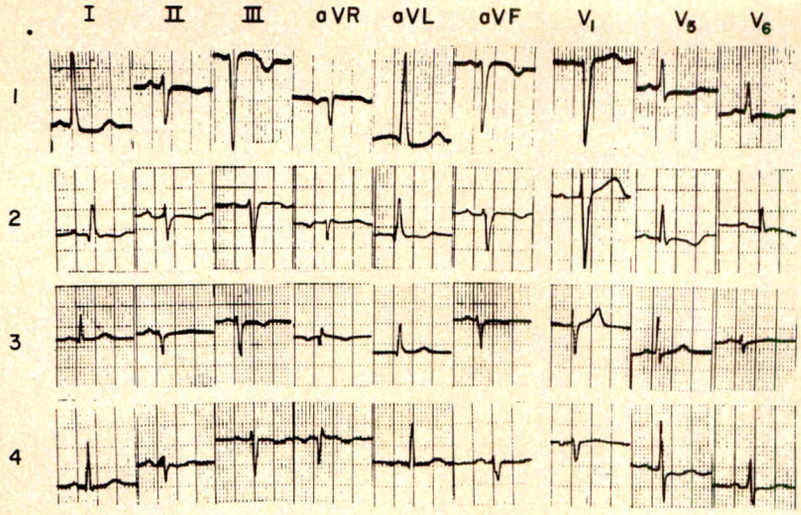

FIGURE 1. Preoperative electrocardiograms of the four patients with left anterior fascicular block.

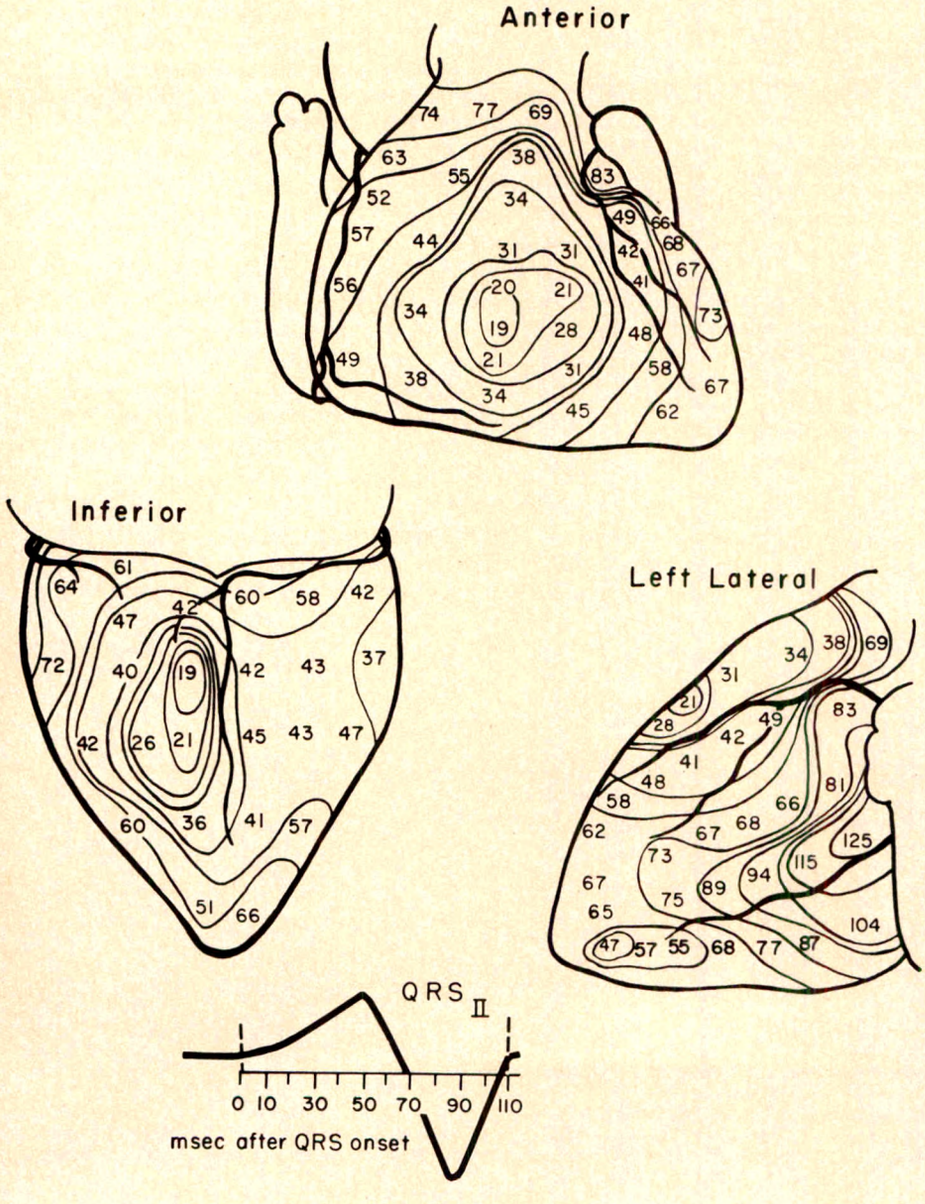

FIGURE 2. Epicardial map from Patient 1. Anterior, left lateral and inferior views are shown. A zone of overlap is present between the anterior and left lateral views in the region of the left anterior descending coronary artery. Numbers reflect the timing (msec) of arrival of local activation at each bipolar recording site. The QRS complex in lead II is displayed above the time scale in milliseconds. Normal anterior right ventricular (19 msec), inferior left ventricular (19 msec) and apical anterolateral left ventricular (47 msec) epicardial breakthrough sites are shown. The occurrence of the latest right ventricular (77 msec) and abnormal basal anterolateral left ventricular (125 msec) activation is shown.

for each data point explored, time zero being the onset of the QRS complex. Right ventricular activation was normal, a single anterior right ventricular breakthrough being observed 19 msec after the onset of the QRS complex. Left ventricular activation was abnormal. The earliest left ventricular epicardial breakthrough was seen inferiorly 19 msec after onset of the QRS complex and considerably later in the anterolateral apical region at 47 msec (Fig. 2, left lateral). The normal left ventricular epicardial breakthroughs in the basal region of the anterolateral left ventricle were absent.[21] The latest right ventricular epicardial activation occurred normally in the outflow tract region 77 msec after QRS onset (Fig. 2, anterior). The latest left ventricular activation was abnormal in site and occurred in the basal anterolateral left ventricle, 125 msec after onset of the QRS complex, which occurred 15 msec after the end of the visible QRS complex in the surface leads (Fig. 2, left lateral).

Epicardial breakthrough (Table I, Fig. 3): All sites of epicardial breakthrough in the four patients are shown in Figure 3. Right ventricular epicardial breakthrough was normal in all four patients, occurring in the anterior wall adjacent to the septum, 19 to 28 (mean 22) msec after onset of the QRS complex; three of the four patients showed breakthrough in the inferior right ventricle at 29 to 37 (mean 34) msec (one patient demonstrated two inferior breakthroughs). Left ventricular epicardial activation was normal in the inferior wall in all patients, seven breakthroughs occurring in the four patients, 19 to 50 (mean 33) msec after onset of the QRS complex. Only two patients showed the apical anterolateral left ventricular breakthrough shown in Figure 2 (it occurred 38 and 47 msec, respectively, after onset of the QRS complex). None of the four patients manifested the normally present basal anterolateral left ventricular epicardial breakthrough.

Latest epicardial activation (Table I, Fig. 4): The site of latest epicardial activation in the four patients is shown in Figure 4. The latest right ventricular activation was normal in site and timing in all patients, occurring in two patients in the outflow region, and in one patient each in the anterobasal and the posterobasal region, respectively, 77 to 88 (mean 82) msec after onset of the QRS complex. In two patients (Cases 3 and 4) who had a normal QRS duration, the site of latest right ventricular activation was also the latest area to be activated in the epicardium as a whole.

The latest left ventricular epicardial activation was abnormal in all patients. The site of latest activation was invariably in the basal anterolateral left ventricle anterior to the obtuse margin (Fig. 4). This occurred 68 to 125 (mean 97) msec after onset of the QRS complex. In two patients (Cases 1 and 2) with a slightly prolonged QRS duration, this site on the left ventricle was also the latest site on the ventricular epicardium as a whole, and corresponded closely with the terminal forces of the QRS complexes, occurring within 15 msec of the end of the visible QRS inscription in the electrocardiogram.

Rapidity of late epicardial activation: With the limitation that no spatial measurements were made between recording sites in this study, one can derive a crude estimate of wave front velocity on the epicardial surface by noting the relative spacing of successive isochrones.[22] Crowding of isochrones has been thought to indicate slower conduction of impulses and widely spaced isochrones to imply more rapidly conducting

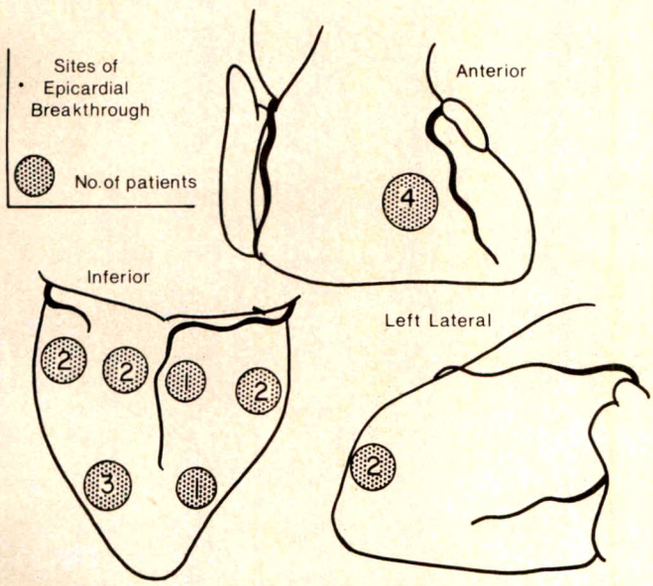

FIGURE 3. Summary of epicardial breakthrough events. Cardiac views as for Figure 2. Each **circle** represents a site where breakthrough occurred. The numbers represent the number of patients having an epicardial breakthrough event at each site. Note the absence of breakthroughs in the basal segments of the anterolateral left ventricle.

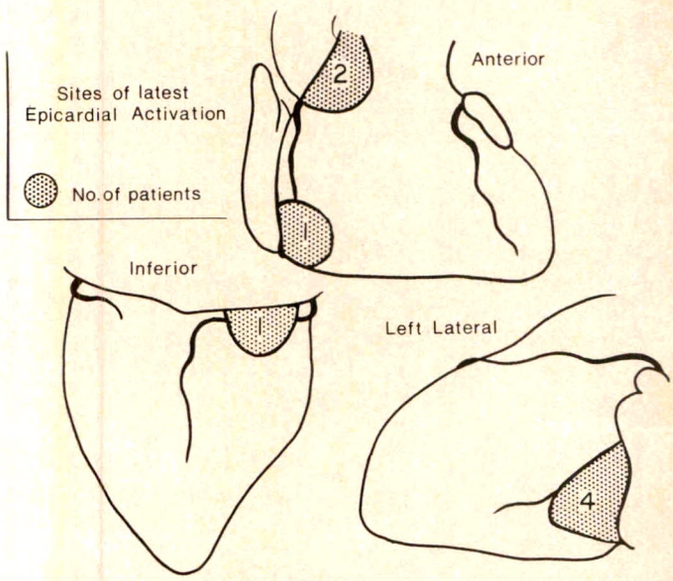

FIGURE 4. Summary of sites of latest epicardial activation. Cardiac views as for Figure 2. Each area encircled represents a site of latest epicardial activation on the right and left ventricles. The numbers represent the number of patients whose latest epicardial activation occurred at each site.

wave fronts in the plane of the epicardial surface.[22] In three of our four patients, we observed relative crowding of isochrones in the basal anterolateral left ventricle, compared with the basal areas of the remaining portions of the left and right ventricles (Fig. 2). However, in the fourth patient (Case 3) there was no evidence of pronounced slowing in this region relative to other basal regions of the heart.

Discussion

Experimental production of left anterior fascicular block: The popularization of the concept of a "trifascicular" intraventricular conduction system by Rosenbaum et al.[4] represents a synthesis of considerable experimental and clinical data collected over a period of 70 years, dating from the experimental production of bundle branch blocks in the dog by Eppinger and Rothberger.[6] Rothberger and Winterberg[7] subsequently demonstrated axis changes after severance of the anterior and posterior divisions of the canine left bundle branch. Smith et al.,[9] in 1954, published results of acute segmental and diffuse lesions of the right and left bundle branches. Segmental lesions of the left bundle branch, although producing definite changes in epicardial activation sequence, had little effect on limb leads in most animals. However, Watt et al.[11] showed that experimental left anterior divisional block in dogs and primates, with or without right bundle branch block, resulted in a superior and anterior shift in mean QRS electrical axis, delay in anterior left ventricular epicardial activation by 30 to 40 msec and a shift in the normal anterior paraseptal left ventricular epicardial breakthrough toward the apex. Most recently, Gallagher et al.,[12] utilizing intramural, endocardial and epicardial recordings, showed that division of the anterior left bundle fibers in the dog uniformly produced delays of 6 to 20 msec in the blocked Purkinje fibers, 3 to 25 msec delays in the associated endocardial areas and 4 to 25 msec delays in the epicardial surface, confined to the lateral basal surface of the left ventricle. When lesions were placed in the septal ramifications of the left bundle branch, in addition to the left anterior division, epicardial surface delays of greater magnitude (7 to 35 msec) and area of distribution as well as marked left axis deviation were encountered.

Clinical observations on left axis deviation and "hemiblock": In regard to clinical electrocardiology, Wilson et al.[1] suggested that the rS complexes in leads II and III in three patients might reflect the presence of block in the anterior division of the left bundle branch. Grant,[2] and Pryor and Blount[3] suggested that block or delay of the left anterior division is the most common cause of left axis deviation. Rosenbaum et al.,[4] in their clinical and electrocardiographic studies of patients with chronic Chagasic cardiomyopathy, and coronary, hypertensive and aortic valve disease, concluded that left axis deviation of −45°, or more negative, separated the greatest number of cases of left anterior "hemiblock" from the greatest number of cases of left axis deviation unrelated to conduction disturbances. Histopathologic studies in human beings[2,13–18] have shown that marked left axis deviation is accompanied by widespread disease of the left bundle branch system, not necessarily restricted to the anterior fibers. Surgical injury to the anterior portion of the left bundle branch has produced left axis deviation.[23]

Controversy persists, however. Some experienced electrocardiographers have expressed doubt as to the validity of the widespread use of the term "left anterior hemiblock" to describe various patterns of left axis deviation.[24] Nevertheless others[25] have stated that it is not even necessary to require that the electrocardiogram show initial Q waves in lead I and aVL for a diagnosis of left anterior hemiblock. It has also been shown[26] that discrete lesions that affect the nonbranching portion of the bundle of His without affecting bundle branch tissue may produce functional disturbance in fascicles.

Interpretation of present results: Our study was designed to show whether epicardial activation patterns in patients with marked left axis deviation would show changes consistent with left anterior fascicular block. We used for comparison our previously described pattern of epicardial activation in 11 patients without intraventricular conduction defects.[21] In those patients, three to five epicardial breakthrough events were identified in all, the first invariably occurring in the anterior paraseptal right ventricle, 7 to 25 (mean 17) msec after onset of the QRS complex, followed by breakthroughs in the inferior right, inferior left and anterolateral left ventricle. Of particular relevance to this study is the fact that all but one patient without conduction defect had at least one breakthrough in the anterolateral left ventricle. Ten of the 13 anterolateral left ventricular breakthroughs in the 11 patients were in the basal region, near either the septum or the obtuse margin, the other 3 being near the apex. None of our four patients had a basal anterolateral left ventricular breakthrough. Two patients with left axis deviation had an apical anterolateral breakthrough (Fig. 2, Table I), a finding consistent with the previously cited short term experiment of Watt et al.[11] In our previously studied 11 patients with no conduction defect the latest epicardial activation was distributed along the basal rim of right or left ventricle at all sites with the exception of the anterolateral basal left ventricle. In contrast, in all four patients in the present series with left axis deviation the latest left ventricular activation occurred in the basal anterolateral left ventricle. Comparison of the corresponding recording sites in the 11 patients with no conduction defect[21] and in the 4 with marked left axis deviation revealed that equivalent sites in the basal anterolateral left ventricle were activated a mean of 47 msec later in the latter group.

These findings are best interpreted as reflecting a delay in initial endocardial activation of the basal anterolateral left ventricle, with late activation and local delay (as reflected by crowding of isochrones) in this region, after normal activation of the right ventricle and the inferior left ventricle. The findings are consistent with block or delay in the anterosuperior divisional fi-

bers (anterior border fibers of Lazzara et al.[27]) of the left bundle branch as the cause of the marked left axis deviation in our four patients with coronary artery disease. We interpret the persistence of apical anterolateral left ventricular and inferior left ventricular breakthroughs as representing intact conduction by way of posterior or septal ramifications, or both, of the left bundle branch.[27,28]

The timing of the latest recordable epicardial activity in our patients, relative to the terminal forces of the QRS complex, deserves some comment. In the two patients (Cases 3 and 4) with normal QRS duration, terminal left ventricular epicardial activation preceded the end of the QRS complex by 10 and 32 msec, respectively. In these two patients, right ventricular epicardial activity accompanied the terminal QRS complex. Rosenbaum et al.[4] stated that uncomplicated left anterior "hemiblock" never increases the QRS duration by more than 0.02 second, and that in approximately half of their cases of left anterior "hemiblock" the QRS duration was 0.06 to 0.08 second.[4] Our Cases 3 and 4 would seem to be typical of this group. However, more than one fourth of Rosenbaum's patients with left anterior "hemiblock" had a QRS complex of 0.10 to 0.13 second. This degree of widening was attributed to a concomitant abnormality, such as left ventricular hypertrophy or infarction.[4] In our two patients (Cases 1 and 2) with QRS widening of 0.11 second the latest recordable left ventricular activity occurred 15 and 14 msec, respectively, after the end of the QRS complex in surface leads. These two patients may well have had additional intraventricular delay secondary to diffuse left ventricular disease. Patient 1 (Fig. 2) had a long history of labile hypertension, and the left ventriculogram showed a hypercontractile ventricle. Patient 2 had a diffusely moderately hypocontractile left ventricle with an ejection fraction of 30 percent. In contrast, the two patients with normal QRS duration had a normal left ventriculogram.

. Comparison of human and canine data: Our data in human subjects with left anterior fascicular block compares and contrasts with data from the experimental acute left anterior divisional blocks in dogs, best exemplified by the study of Gallagher et al.[12] Absolute activation times to equivalent recording sites tend to be longer in the normal human heart than in the heart of the dog.[29] The normal epicardial breakthrough events are less complex in the dog, as reflected by the preoperative epicardial maps in the study of Gallagher et al.,[12] which typically did not show anterolateral left ventricular breakthrough. Thus, the absence of normal early activation of the anterolateral left ventricle, characterizing human left anterior fascicular block, is not so easily detectable in the dog, if one relies solely on epicardial breakthrough phenomena. However, there is good agreement between the canine data and our results regarding the site of late left ventricular activation, namely, the basal portion of the anterolateral wall. As with normal epicardial data in human beings, the absolute timing of this late activation is distinctly later than in the dog with acute left anterior fascicular block. Because we obtained no data from the endocardium or intramural sites within the blocked segment of the left ventricle, we are unable with certainty to differentiate true anterior fascicular block or delay from an identical epicardial activation sequence due to localized intramural block,[12,30] and we agree with others[16,18,26–28] that it is probably an oversimplification to consider the left intraventricular conduction system as consisting of two discrete subdivisions as popularly taught.[4]

Clinical implications: Our findings lend further weight to the concept of electrocardiographic left anterior fascicular block. Electrocardiograms showing the pattern of left anterior fascicular block correlate with the presence of focal delay in activation of the basal anterolateral left ventricular wall. A further implication of this study is relevant to the surgical management of ventricular tachycardia. Spurrell et al.[23] reported the abolition of a reentrant left ventricular tachycardia by an incision in the left ventricle that probably severed the anterior divisional fibers of the left bundle branch. Postoperative epicardial mapping of conducted beats in such patients should provide evidence of damage to or interruption of the fibers of the anterior fascicle.

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Left Anterior Fascicular Block: Electrocardiographic Criteria For Its Recognition in the Presence of Inferior Myocardial Infarction

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Although the vectorcardiographic criteria for recognizing left anterior fascicular block in the presence of inferior myocardial infarction are well established, comparable electrocardiographic criteria have not been studied. From vectorcardiographic criteria, it was hypothesized that in patients with left axis deviation but without bundle branch block the presence of a deep negative terminal deflection (S wave) in lead II accompanied by a positive terminal deflection (r wave) in lead aVR should indicate left anterior fascicular block whether or not inferior infarction is present. The electrocardiograms of 75 patients with unequivocal vectorcardiographic evidence of either left anterior fascicular block or inferior infarction, or both, were reviewed. Of the 47 patients who met strict vectorcardiographic criteria for left anterior fascicular block, 44 (94 percent) showed the predicted electrocardiographic pattern, including 24 of 26 (92 percent) who had both this conduction defect and inferior myocardial infarction. There was only one patient with vectorcardiographic evidence of inferior myocardial infarction alone with the findings of left axis deviation and the electrocardiographic pattern of combined infarction and fascicular block (that is, only one false positive). Thus, if bundle branch block is excluded, the proposed electrocardiographic pattern permits recognition of left anterior fascicular block whether or not there is coexistent inferior myocardial infarction.

The left bundle branch has two functionally distinct components or fascicles. Conduction disturbances in the anterior-superior fascicle of the left bundle are common. Rosenbaum and his co-workers[1,2] popularized the term hemiblock, but it is currently recommended[3] that this disturbance be called left anterior fascicular block. The inconsistency in nomenclature is further complicated by the fact that conduction delay in the *anterior* fascicle causes a *superior* deviation of forces termed left axis deviation.[4]

Despite some variability in specific criteria, the electrocardiographic features of left anterior fascicular block are fairly well established.[2,5–7] These established electrocardiographic criteria emphasize a leftward deviation of the mean (frontal) QRS axis and the concomitant presence of normal initial forces, including initial positive deflections (r waves) in the inferior leads (II, III and aVF). Thus, with current electrocardiographic criteria, left anterior fascicular block cannot be reliably diagnosed in patients with inferior myocardial infarction manifested by Q waves in leads II, III and aVF. In patients with ischemic heart disease, both left anterior fascicular block and inferior myocardial infarction are common electrocardiographic abnormalities and each may

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cause left axis deviation. The relatively frequent concurrence of these two common abnormalities is predictable and adds to the difficulty in the differential diagnosis of patients with left axis deviation.

Vectorcardiographic criteria have been established that permit the recognition of a conduction delay in the left anterior fascicle whether or not there is an associated inferior myocardial infarction.[8–10] Although Castellanos et al.[9,11] suggest some electrocardiographic clues, there are no firmly established electrocardiographic criteria for the recognition of left anterior fascicular block in the presence of an inferior myocardial infarction. Utilizing the existing vectorcardiographic criteria and Grant's spatial vector method,[12] we propose electrocardiographic criteria that will permit the recognition of left anterior fascicular block whether or not there is an accompanying inferior myocardial infarction. To evaluate these criteria, we reviewed the electrocardiographic findings in a series of patients with established vectorcardiographic diagnoses of isolated left anterior fascicular block, isolated inferior myocardial infarction or both of these conditions.

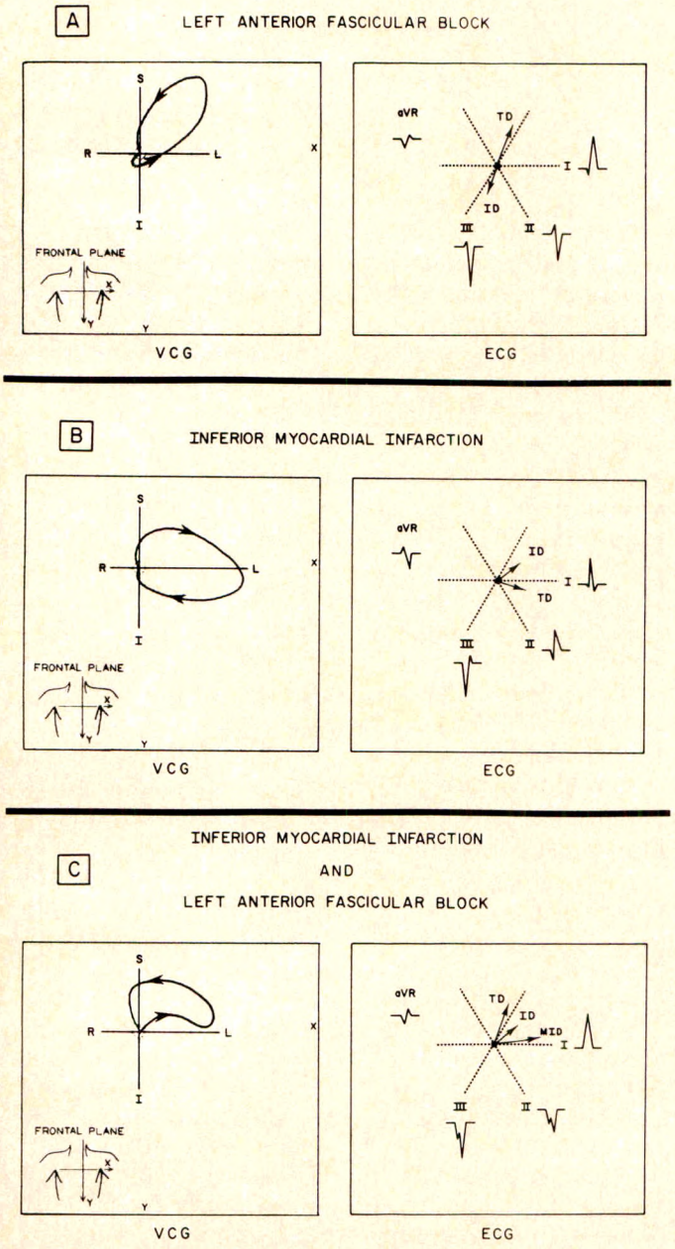

FIGURE 1. Diagrams showing frontal plane vectorcardiographic (VCG) and electrocardiographic (ECG) patterns for left anterior fascicular block, inferior myocardial infarction and both conditions. In the vectorcardiogram, I = inferior; L = left; R = right; S = superior; X and Y indicate the axes, and the **arrowheads** indicate the direction of rotation of the QRS loop. On the electrocardiogram, the QRS spatial vectors are indicated as ID for initial deflection, MID for mid forces and TD for terminal deflection. Leads I, II, III and aVR are shown.

Methods

Hypothesis: The classic vectorcardiographic pattern (frontal plane) and the accompanying spatial vector and standard lead (frontal) electrocardiographic patterns for left anterior fascicular block alone, inferior myocardial infarction alone and the combination of both patterns are shown diagrammatically in Figure 1. This illustration reveals that the markedly superior and counterclockwise rotation of the terminal QRS forces in left anterior fascicular block can be identified vectorcardiographically whether or not inferior myocardial infarction is present. From the location of the terminal superior forces, it can be deduced that the terminal portion of the QRS complex in the standard electrocardiogram should show a deep negative deflection (S wave) in lead II usually accompanied by a small positive terminal deflection (r wave) in lead aVR.

Terminal rightward forces characteristic of right bundle branch block might result in a similar pattern. Left bundle branch block tends to alter both initial and terminal QRS forces. Therefore, both right and left bundle branch block should be excluded before these criteria are utilized. In addition, patients with an inferiorly directed mean QRS axis may have terminal forces directed to the right, resulting in a small negative terminal deflection in lead II and a small positive terminal deflection in lead aVR that might also be confused with the suggested pattern. Thus, we propose that, in the absence of bundle branch block, the finding of a mean QRS axis between 0° and −90° with a deep negative terminal deflection in lead II and an accompanying positive terminal deflection in lead aVR should indicate the presence of left anterior fascicular block whether or not there is an associated inferior myocardial infarction.

Patient selection: The vectorcardiographic files of the Baltimore Veterans Administration Medical Center were reviewed, and 75 patients with vectorcardiograms demonstrating unequivocal evidence of left anterior fascicular block alone, inferior myocardial infarction alone or both patterns were selected for study. The corresponding electrocardiograms were identified and reviewed. The patients were all men whose ages ranged from 38 to 88 years (mean age 59).

Recording methods: Vectorcardiograms were recorded using the Frank lead system and a high fidelity direct-writing (X-Y recorder) vectorcardiograph (Instruments for Cardiac Research, Inc., model VCG-1B). Electrocardiograms were recorded on a standard three channel electrocardiographic instrument (Hewlett Packard, model 1515B). The electrocardiograms were analyzed for mean frontal QRS axis and the direction of terminal forces in leads II and aVR. Two inves-

tigators (M.L.F. and M.A.M.) did this separately and without knowledge of the vectorcardiographic findings.

Vectorcardiographic criteria[8–10,12–16]: Patients were selected and grouped as follows:

Group I: Left anterior fascicular block (21 patients): Inclusion in this group required that the frontal plane vectorcardiogram showed (1) initial forces between 0° and +180°; (2) a maximal leftward deflection above 0°; (3) the afferent loop beginning at −90° ± 20°; (4) counterclockwise rotation of the QRS loop; and (5) a QRS duration less than 120 msec (usually less than 100 msec).

Group II: Inferior myocardial infarction (28 patients): The diagnosis of inferior myocardial infarction required the following vectorcardiographic features: (1) initial forces directed superiorly with clockwise rotation of this portion of the loop; (2) a maximal frontal plane vector of less than 10°, *and* (3) either more than 25 of the first 35 msec being superior *or* the 20 msec vector in the sagittal plane being less than 315°; and (4) a maximal early superior vector exceeding 0.3 mv along the x axis, *or* (5) a ratio of voltages between the 0 to left x intercept and the maximal QRS vector exceeding 0.22 in the frontal plane.

Group III: Inferior myocardial infarction with left anterior fascicular block (26 patients): The following vectorcardiographic criteria were required for recognition of these combined abnormalities: (1) initial forces directed superiorly (or inferiorly for less than 20 msec) with initial clockwise rotation of the loop and fulfilling criteria 2 to 5 for inferior myocardial infarction alone; and (2) terminal forces (after 40 msec) exhibiting superior and counterclockwise rotation fulfilling criteria 4 and 5 for left anterior fascicular block alone.

Results

The electrocardiographic findings in the 75 patients studied are summarized in Table I. The 28 patients with inferior myocardial infarction alone (Group II) were classified in subgroups on the basis of the mean frontal plane electrocardiographic axis. All patients with left anterior fascicular block in both Groups I and III had deep negative deflections in lead II, and the vast majority (44 of 47, 94 percent) had a positive terminal deflection in lead aVR. In contrast, only two patients with inferior myocardial infarction alone had both of these electrocardiographic findings. One of these patients had an inferiorly directed mean QRS axis making a diagnosis of left anterior fascicular block untenable. Thus, there was only a single false positive electrocardiographic diagnosis of left anterior fascicular block utilizing our proposed criteria. The electrocardiograms of three patients (6 percent) who did not have a terminal positive deflection in lead aVR constitute the false negative group. To illustrate our proposed pattern, a typical frontal plane vectorcardiogram and the accompanying electrocardiogram are shown in Figure 2.

The frontal plane electrocardiographic axis for each patient in the three groups is plotted in Figure 3. Patients with left anterior fascicular block alone by vectorcardiographic criteria had a QRS axis between −5° and −85° and patients with left anterior fascicular block plus inferior myocardial infarction had an axis between −15° and −90°. With inferior myocardial infarction alone, there was a wide range of mean QRS axes, between −45° and +90°. In this series, patients with extreme superior axis deviation (−60° or above) and previous inferior myocardial infarction consistently had accompanying left anterior fascicular block. However, at lesser degrees of superior axis deviation (less than −45°), there was considerable overlap between patients in Groups II and III. Thus, QRS axis alone in the electrocardiogram cannot be used to recognize reliably combined inferior myocardial infarction and left anterior fascicular block.

Discussion

Both left anterior fascicular block and inferior myocardial infarction are common electrocardiographic diagnoses, and they frequently coexist.[17,18] Electrocardiographic criteria for left anterior fascicular block that include normal initial forces do not permit its recognition when it coexists with inferior infarction. In contrast, vectorcardiographic criteria for left anterior fascicular block are applicable whether or not there is an accompanying inferior infarction.[8–10,13–15] The concept of evolving electrocardiographic criteria for left anterior fascicular block based on vectorcardiographic features is not without precedent.[9,11,19] In response to a letter to the editor, Pryor[19] described the vectorcardiographic features of combined infarction and left anterior fascicular block and hypothesized an electrocardiographic pattern similar to the one we have proposed. Our study documents that this relatively simple

TABLE I

Electrocardiographic Findings in Seventy-five Patients With an Unequivocal Vectorcardiographic Diagnosis

Group	VCG Diagnosis	ECG Axis	Patients (no.)	Terminal Deflection: Negative (S wave) in Lead II	Terminal Deflection: Positive (r wave) in Lead aVR	Terminal Deflection: Both
I	LAFB	−5 to −85°	21	21	20	20
II	IMI	+1 to +90°; 0 to −45°	12; 16	2; 4	5; 3	1; 1
III	IMI + LAFB	−15 to −90°	26	26	24	24

ECG = electrocardiographic; IMI = inferior myocardial infarction; LAFB = left anterior fascicular block; VCG = vectorcardiographic.

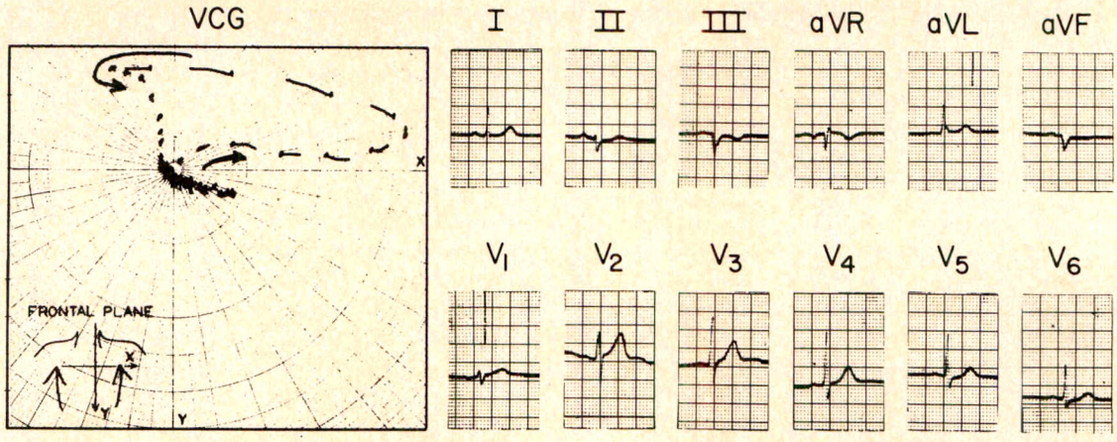

FIGURE 2. Left anterior fascicular block and inferior myocardial infarction. In the frontal plane vectorcardiogram (VCG), the direction of rotation of the QRS loop is indicated by the **arrows**. The initial superior clockwise rotation is evidence of inferior myocardial infarction whereas the markedly superior and counterclockwise terminal forces indicate left anterior fascicular block. The electrocardiographic QRS axis is −45°. The Q waves in leads III and aVF are indicative of inferior infarction. The deep terminal S wave in lead II accompanied by a small terminal r wave in lead aVR indicates left anterior fascicular block.

electrocardiographic pattern is of value in recognizing left anterior fascicular block.

Proposed electrocardiographic diagnostic criteria: The diagnosis of left anterior fascicular block does not depend on a specific (arbitrary) degree of leftward or, more correctly, superior axis deviation. The proposed electrocardiographic criteria require exclusion of right and left bundle branch block, a mean frontal QRS axis between 0 and −90°, a deep terminal S wave in lead II and a terminal positive deflection or r wave in lead aVR. Of the 47 patients who met strict vectorcardiographic criteria for left anterior fascicular block, 44 (94 percent) showed the predicted electrocardiographic pattern, including 24 of 26 (92 percent) who had both fascicular block and inferior infarction. There was only one patient with vectorcardiographic evidence of inferior myocardial infarction alone who showed left axis deviation and the electrocardiographic pattern of both inferior infarctions and left anterior fascicular block (that is, only one false positive).

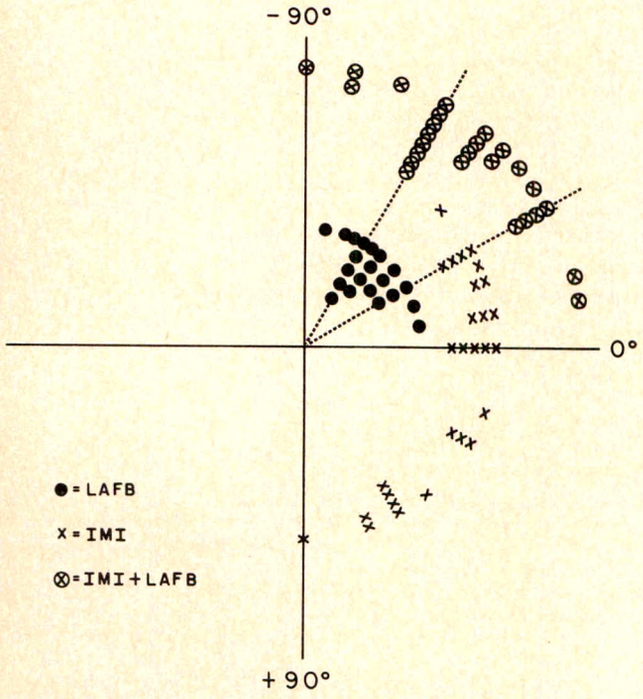

FIGURE 3. The frontal plane electrocardiographic axis for each of the 75 patients is illustrated. The patients are classified into three groups on the basis of the vectorcardiographic diagnosis. IMI = inferior myocardial infarction; LAFB = left anterior fascicular block.

There is no "gold standard" for the diagnosis of left anterior fascicular block because, as indicated by Haft,[20] it is "a diagnosis of physiologic function and in most cases there is no anatomic confirmation possible, even at autopsy." Thus, exact electrocardiographic criteria for left anterior fascicular block will remain controversial.[21] Although vectorcardiography is not a "gold standard," recent reviews[22,23] indicate that it is superior to electrocardiography in the diagnosis of inferior myocardial infarction and other causes of left axis deviation. The high degree of consistency between our proposed electrocardiographic pattern and the vectorcardiographic findings suggests that this pattern should be useful. Because patients with equivocal vectorcardiographic findings were excluded, the exact sensitivity and specificity of our proposed electrocardiographic pattern cannot be defined.

Clinical significance of left anterior fascicular block: The recognition of left anterior fascicular block coexistent with inferior myocardial infarction is clinically relevant. McKeever et al.[18] reported the coronary angiographic findings in patients having previous inferior infarction with and without vectorcardiographic evidence of coexistent left anterior fascicular block. Patients with both patterns had a significantly greater frequency of three vessel coronary disease as well as an

increased likelihood of left anterior descending coronary disease when compared with patients with inferior myocardial infarction alone. McKeever's findings are consistent with Rosenbaum's contention[2] that, in patients with angina pectoris, left anterior fascicular block indicates left anterior descending coronary artery disease.

Criteria for left anterior fascicular block: The use of axis is inadequate to recognize left anterior fascicular block.[24–26] Medrano et al.[27] proposed that left anterior fascicular block can be identified by a delay in the intrinsicoid deflection in lead aVL. Based on this premise, Horwitz et al.[26] compared the intrinsicoid deflections in leads aVL and V_6 in patients with left axis deviation. They concluded that 77 of 360 patients (21 percent) with a QRS axis ranging between 0° and −30° could be classified as having left anterior fascicular block whereas some patients with a QRS axis as superior as −60° had no evidence of delayed activation in lead aVL. Horwitz et al.[26] did not document the sensitivity and specificity of the delayed intrinsicoid deflection in lead aVL. In our patients, there was no apparent delay in the intrinsicoid deflection in lead aVL in 8 of the 47 patients (17 percent) with definite left anterior fascicular block on vectorcardiography. Medrano et al.[27] in their original description of this pattern noted that it was not present in all patients with left anterior fascicular block.

Significance of lead II and aVR configuration: Previous reports on the electrocardiographic findings in left anterior fascicular block noted the configuration

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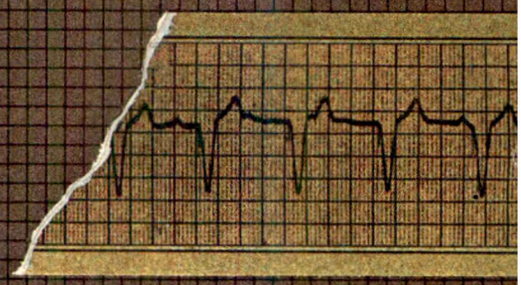

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Intermedics Pulse Generators

INDICATIONS FOR USE Implantable cardiac pulse generators may be indicated for long-term treatment of impulse formation or conduction disorders resulting in symptomatic bradyarrhythmias, tachyarrhythmias, and heart block unresponsive to drug therapy.

PRECAUTIONS Implanted pacemakers have a finite and variable service life as a result of factors such as the initial capacity of the battery and the shelf storage time of the manufactured pacemaker; variations in electrode system resistances, stimulation rate, and the percentage of time the implanted pacemaker is inhibited; and random electronic component failures.

Pacemaker operation can be influenced by electric, magnetic, or electromagnetic energy mimicking normal cardiac activity. In addition, certain environmental sources can couple sufficient energy into a pacemaker system to damage the pulse generator. Specifically, diathermy should not be used on pacemaker patients because of possible total inhibition of the pulse generator; electrocautery can inhibit and/or damage the pacemaker as well as cause burns or possible ventricular fibrillation; defibrillation can damage the pacemaker, and the presence of the pacemaker may cause increased cardiac muscle damage from defibrillation. Microwave ovens that do not exceed federal guidelines for leakage (0.5 W/cm^2 at 2.5 cm from the appliance) will not affect the pacemaker, but leakage in excess of that amount may cause interference. Certain electrical and gasoline-powered appliances can cause inhibition of an implanted cardiac pacemaker system.

For complete precautions, see the Physician's Manual for the Intermedics cardiac pulse generator to be used.

CONTRAINDICATIONS AND SIDE EFFECTS There are no known contraindications to the use of pacemakers as a medical method for control of heart rate. Body rejection phenomena, local tissue reaction or skin necrosis, muscle and nerve stimulation, embolism, and cardiac tamponade have been reported.

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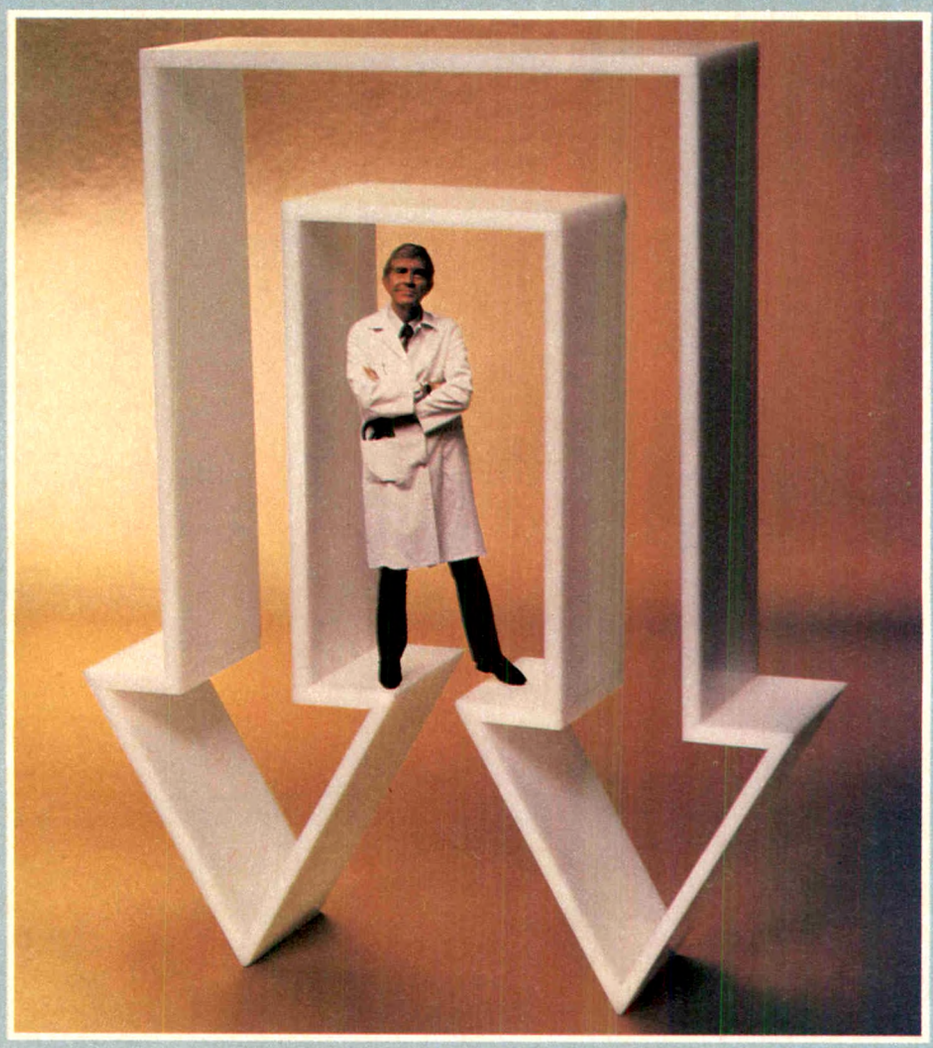

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In most respects, the type, incidence and severity of adverse reactions seen with 'Selacryn' are similar to those seen with thiazides over the years. Standard laboratory tests you use to monitor the course of thiazide therapy are indicated when you prescribe 'Selacryn'.

Reduce Dosage of Concomitant Anticoagulants
'Selacryn' potentiates oral anticoagulants; use caution when using these drugs together. In such patients, reduce the oral anticoagulant to one-quarter or one-half the maintenance dose, monitor prothrombin time through titration until stabilized.

Maintain Adequate Fluid Intake and Urine Flow with Initial Doses
For patients switched to 'Selacryn' from other diuretics, and for dehydrated patients, hydration is recommended for three days before and three days after starting 'Selacryn'. In hypertensive patients, discontinue any previous diuretics for three days prior to instituting 'Selacryn'.

Where feasible, in patients with congestive cardiac failure, discontinue the other diuretic for one to two days before beginning 'Selacryn'. Since initial doses of 'Selacryn' produce diuresis as well as uricosuria, urinary uric acid concentration does not increase in well-hydrated patients who can increase urine flow.

Potassium Supplements Are Usually Not Necessary
but may be advisable in some patients. Since some patients who received 'Selacryn' and Dyrenium® (brand of triamterene) have shown marked elevation of BUN and creatinine, such a combination is not recommended.

See next page for indications and brief summary of prescribing information.

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Before prescribing, see complete prescribing information in SK&F literature. The following is a brief summary.

Indications: Hypertension, with or without elevated uric acid levels. Salt and water retention states associated with congestive cardiac failure.

Contraindications: Anuria, severe or progressive renal disease, hypersensitivity to the drug, known renal uric acid calculi.

Warnings: Potentiates the action of oral anticoagulants; caution should be exercised when these agents are used with 'Selacryn'; reduce anticoagulant dosage to 1/4 or 1/2 of the maintenance dose, and carefully monitor prothrombin time until stabilized.

Concomitant use with triamterene is not recommended since a marked elevation of BUN and creatinine may occur.

Not appropriate in hepatic ascites. May precipitate azotemia in progressive or advanced renal disease; therefore, frequent electrolyte, creatinine and BUN determinations should be performed early in therapy and periodically thereafter. Discontinue the drug if renal impairment progresses.

Pregnancy, Nursing: 'Selacryn' crosses the placental barrier in animals. Routine use of diuretics during normal pregnancy is inappropriate and exposes mother and fetus to unnecessary hazard. Use in pregnancy requires weighing anticipated benefits against possible hazards. Generally, nursing should not be undertaken while a patient is on a drug.

Precautions: Substantial uricosuria occurs within hours after the first dose of 'Selacryn'; for this reason, hypertensive patients switching from other diuretics should discontinue diuretics for 3 days before starting 'Selacryn'; where feasible, diuretics should be discontinued for 1 to 2 days in patients with congestive cardiac failure. Fluid intake should be increased to approximately 1500 cc. per day for up to 3 days before and 3 days after initiation of 'Selacryn' therapy in patients switched to 'Selacryn' from other diuretics and in patients who may be dehydrated, particularly if the patients are hyperuricemic.

Acute attacks of gout may be precipitated; continue 'Selacryn' (brand of ticrynafen), add colchicine. Observe patients for signs of electrolyte imbalance, i.e., hypokalemia, hyponatremia, hypochloremic alkalosis. Periodic determinations of electrolytes to detect possible imbalance should be performed. Concomitant use with cytotoxic agents requires caution and individualization of dosage and management. Effects on glucose metabolism are similar to those seen with thiazides. Insulin requirements may be affected; hyperglycemia and glycosuria may occur in patients with latent diabetes. Elevation of BUN and/or serum creatinine can occur during diuretic therapy.

Children: Safety and effectiveness in children have not been established.

Drug Interactions: Exercise caution when administering with other highly protein-bound drugs, especially anticoagulants; reduce anticoagulant dose to 1/4 or 1/2 of the maintenance dose and carefully monitor prothrombin time until stabilized. (See Warnings.) Concomitant use with triamterene is not recommended since a marked elevation of BUN and creatinine may occur.

The drug causes a decrease in excretion of salicylates and organic acids, e.g., penicillin. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Adverse reactions seen with 'Selacryn' (brand of ticrynafen) in controlled studies were approximately the same as those seen with hydrochlorothiazide. Except where noted, the following adverse effects seen with 'Selacryn' have been reported in a small number of patients, e.g., approximately 1 in 100: anorexia, nausea, vomiting, dyspepsia, cramping, diarrhea, constipation, headache (approximately 4 in 100), dizziness/lightheadedness (approximately 9 in 100), paresthesia, somnolence, insomnia, syncope, vertigo, orthostatic hypotension, palpitation, rash, urticaria, pruritus, rare cases of fever and interstitial nephritis. Tiredness/fatigue (approximately 4 in 100), hyperglycemia, glycosuria, muscle cramps, weakness, bitter taste and dryness in mouth, exacerbation of gout, renal colic or costovertebral pain. Abnormal liver function tests and jaundice have been reported in a few patients.

The following adverse reactions have not been reported to date with 'Selacryn' but have occurred with thiazides or other diuretics: pancreatitis, sialadenitis, xanthopsia, purpura, photosensitivity, necrotizing angiitis, Stevens-Johnson syndrome, respiratory distress, anaphylactic reaction, leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, restlessness and transient blurred vision.

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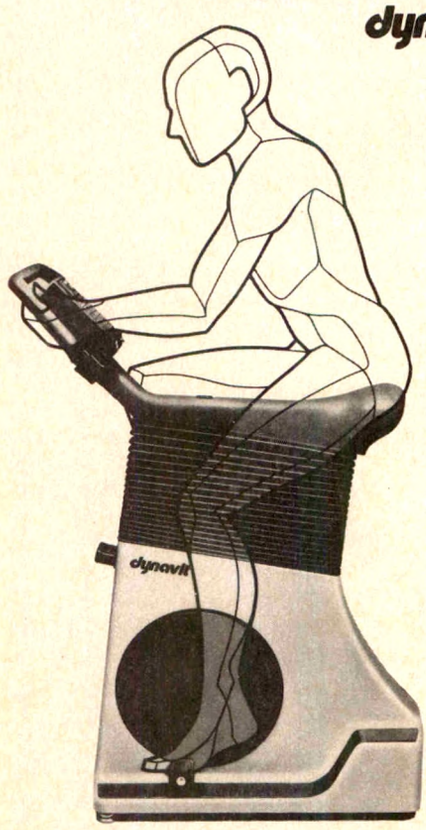

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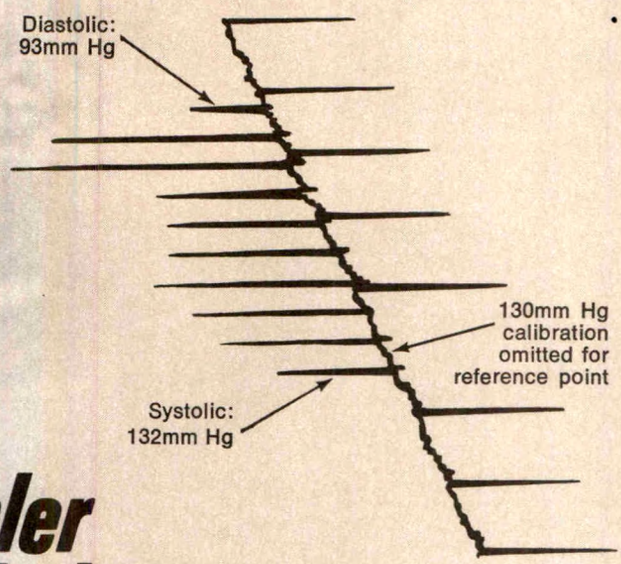

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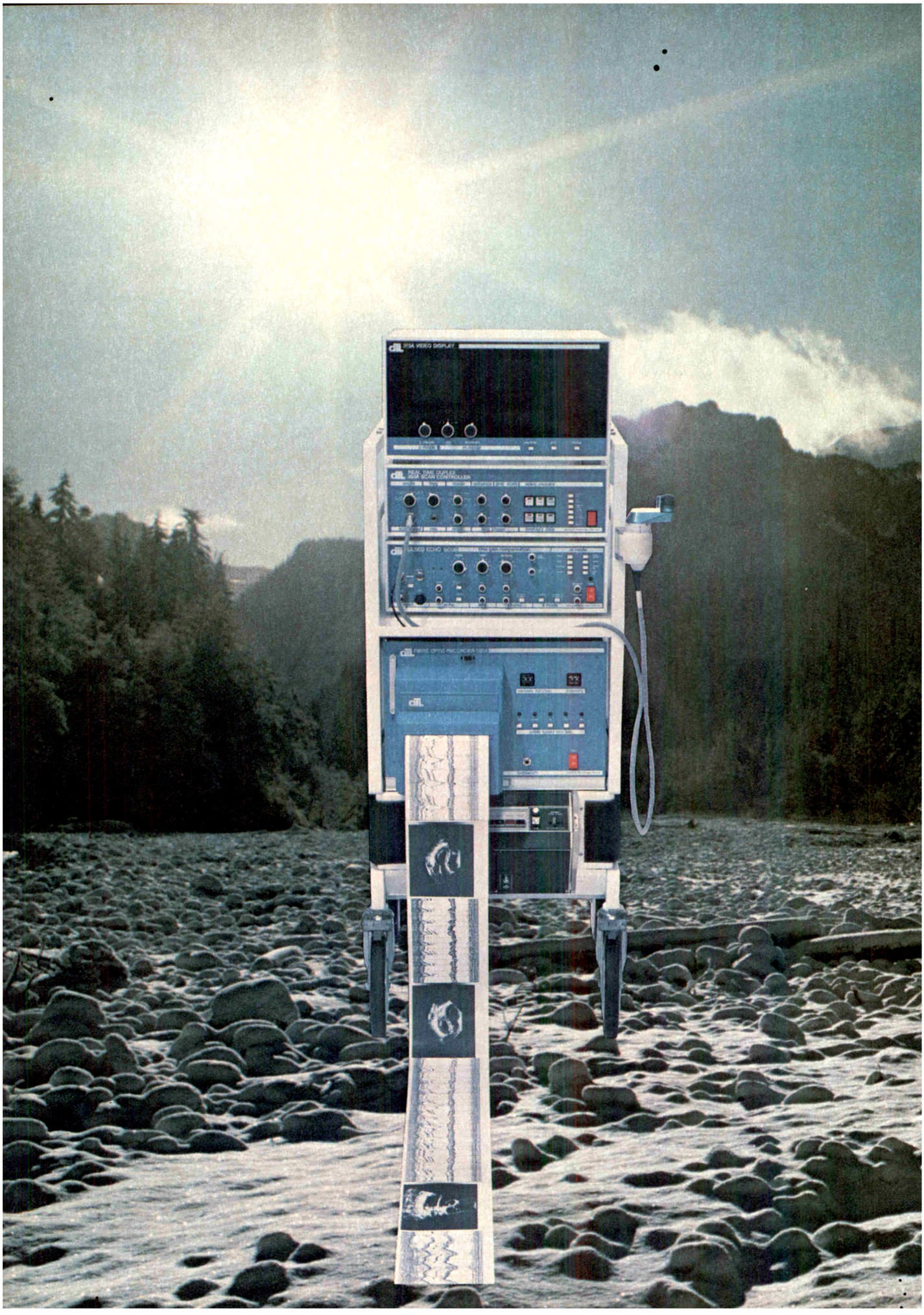
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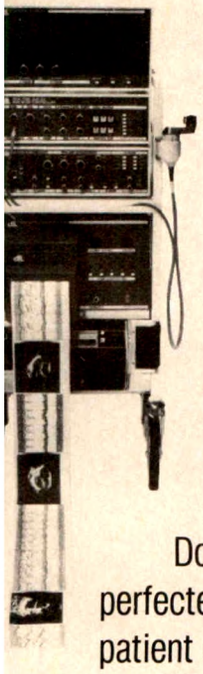

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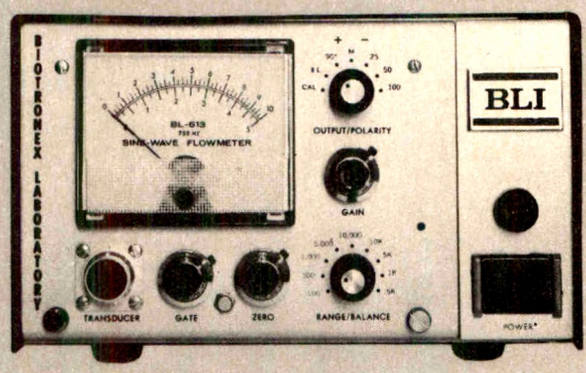

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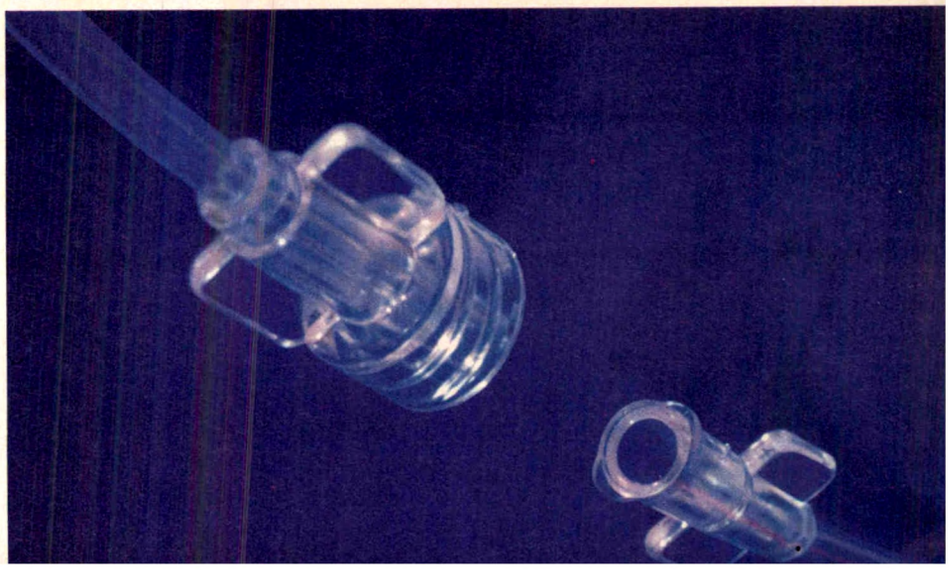

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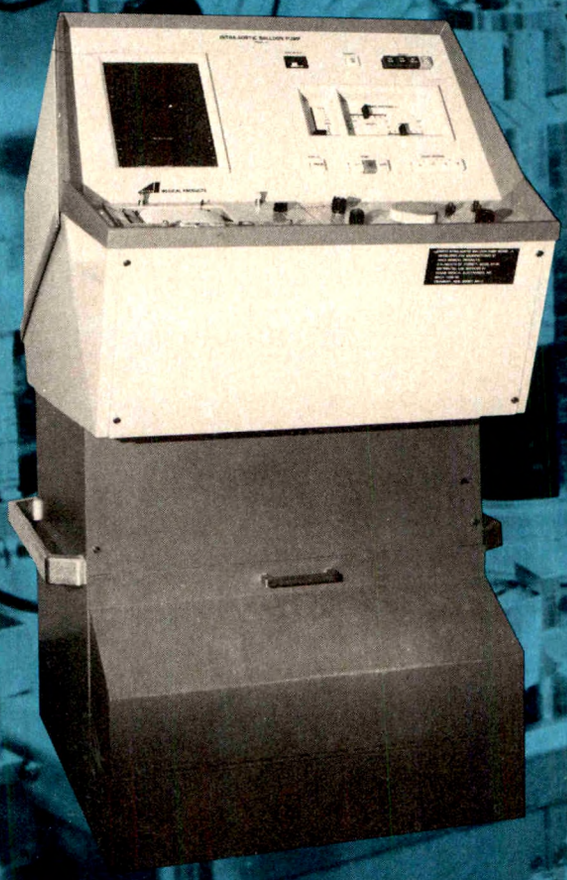

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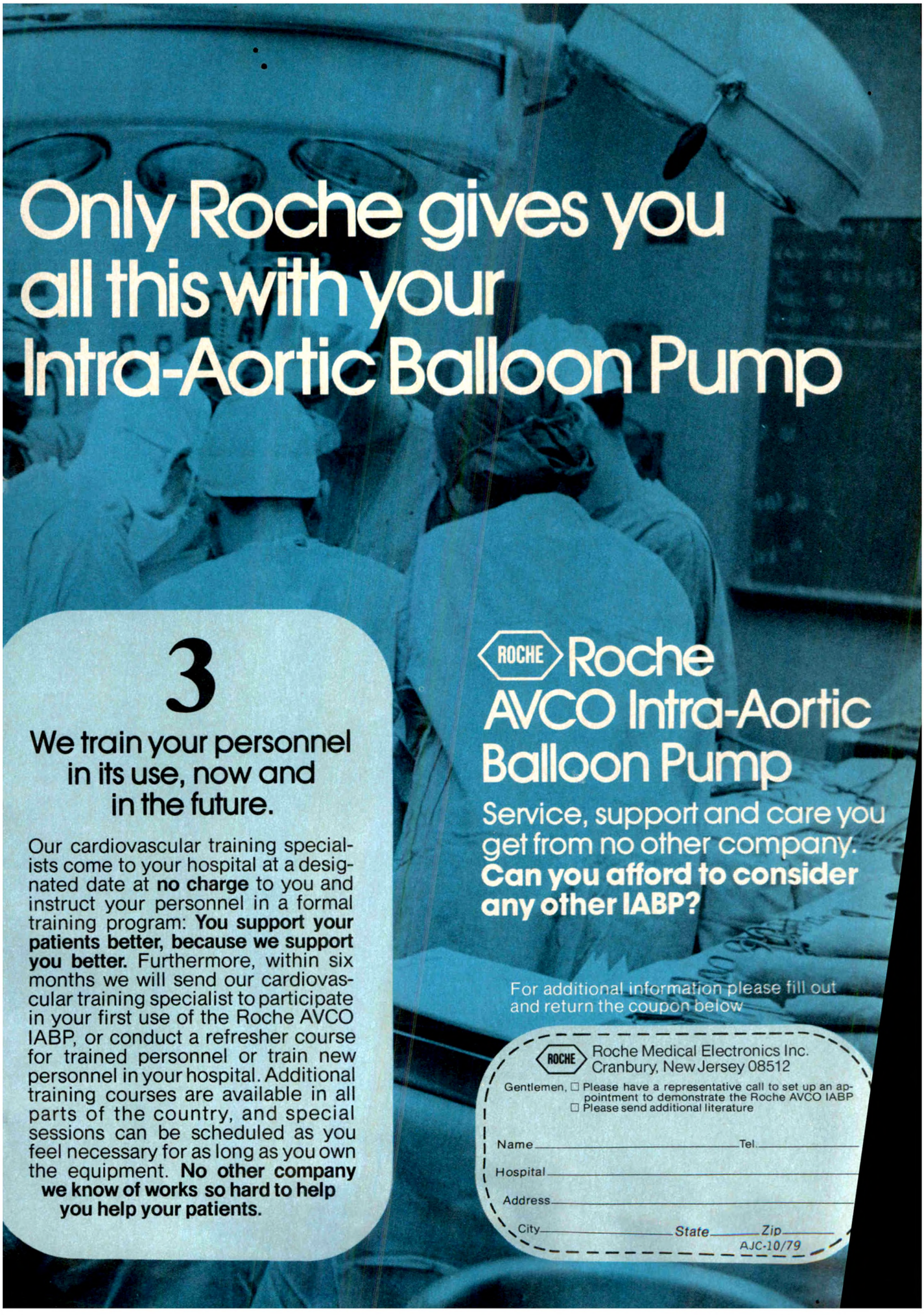

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Karl T. Weber, MD, FACC, Guest Editor

Introduction: Physiologic and Clinical Correlates

KARL T. WEBER, MD, FACC

Philadelphia, Pennsylvania

In 1885 Yeo[1] reported a series of observations that were to have a major influence on our view of oxygen utilization by the working heart. Using an isolated frog heart perfused by an oxyhemoglobin solution (Fig. 1) and a spectroscope Yeo was able to demonstrate that the beating heart consumed six times the oxygen of its quiescent counterpart. From this time forward the issue of myocardial oxygen utilization in the working heart has been the subject of much interest.

The work of the heart is continuous. Even when the remainder of the organism is at rest, the myocardium must generate force and shorten. However, unlike skeletal muscle, this muscular pump cannot work in the absence of oxygen; without oxygen, its energy production falters and its performance rapidly deteriorates within seconds.[2] As a result, an oxygen debt cannot be contracted. Thus, this obligate aerobic organ must continuously sustain aerobic metabolism in order to function.

The heart normally appears well suited for continuous aerobic work[3,4] for the following reasons: (1) its concentration of oxidative enzymes is the highest of any tissue in the body; (2) its mitochondria, which are the major sites of oxidative phosphorylation, are present in great profusion throughout the cell, constituting 25 to 30 percent of the entire cell mass; (3) a large fraction of the oxygen that traverses its coronary circulation is extracted; and (4) its rich vascular network affords each fiber with a capillary. Unfortunately, what appears to be a comfortable reserve in oxygen availability in the normal heart may not hold true for the heart subjected to chronic elevations in work. Sustained increments in mechanical work are accompanied by a series of compensatory mechanisms, including hypertrophy of the muscular wall, as well as an increased expenditure of chemical energy. However, these responses have certain limitations and thus it is possible, although unproved, that chronic overloading creates a requirement for oxygen that may eventually surpass the aerobic capacity of the heart. In this connection, the diffusion distance for oxygen from capillary to mitochondria[5] may also be critically increased in the hypertrophied heart.

Because of its singular arterial blood supply and major efferent venous drainage site, the oxygen utilized

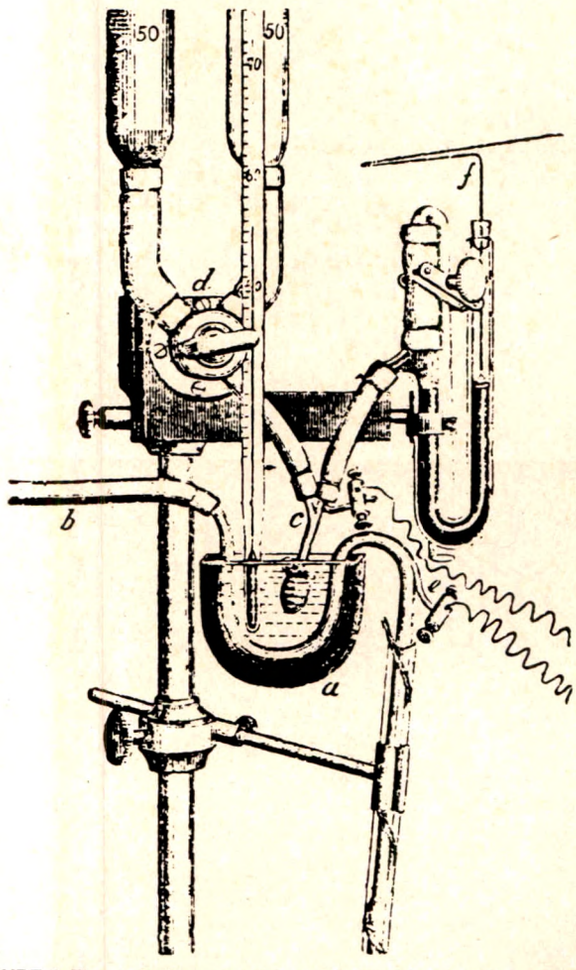

FIGURE 1. The perfusion apparatus and isolated frog heart preparation of Yeo[1] (reproduced by permission).

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by the left ventricle can readily be determined from a knowledge of the arteriovenous oxygen difference and the coronary blood flow.[6] Recent advances in technology[7] and findings in the diseased heart[8–10] have generated renewed interest in the role that oxygen availability may play in the onset and progression of the failing heart. It was this stimulus that brought a group of us together to exchange ideas and information. The reports included in this Seminar[11–14] represent an outgrowth of these discussions.

Interrelation between oxygen demand and supply of the heart: The first paper of the Seminar[11] addresses itself to the interrelation between the oxygen demand and supply of the heart. Evidence is presented to indicate that each of the major determinants of myocardial oxygen consumption (MVO_2) are related to several components of systolic wall force. The responses in the integral of systolic force per minute and the peak rate of force development serve to explain the alteration in MVO_2 that occurs when left ventricular chamber pressure or volume, myocardial contractile state or heart rate is altered. Oxygen supply, on the other hand, is a function of adjustments in coronary vascular resistance and oxygen extraction that occur during variations in work and together represent the metabolic reserve of the heart. As metabolic demand is increased, a limit to oxygen availability (that is, the aerobic limit of the heart) is eventually reached and is identified by the onset of myocardial lactate production. As a result of this hypoxia myocardial contractility decreases but, of equal importance, pulsus alternans appears. Finally, the oxygen utilization of the hypertrophied, failing heart is reviewed and inferences are drawn as to the importance of an exhausted metabolic reserve in causing the failure state.

MVO_2 and ventricular dynamics in the hypertrophied diseased heart: In the next paper, Strauer[12] reviews his observations on MVO_2 and ventricular dynamics in a large number of patients with chronic hypertrophic heart disease of various causes. Strauer undertook to determine to what extent the degree of hypertrophy and chamber dilatation influence the oxygen requirements of the chronically diseased heart by examining the interrelation between MVO_2 and left ventricular mass, chamber volume, mass to volume ratio and systolic wall stress. His findings indicated that MVO_2 is closely related to systolic wall force, expressed per cross-sectional area of left ventricular myocardium (that is, systolic wall stress), and left ventricular mass. In addition, he found that the coronary vascular reserve of the patients studied, as judged from the increment in coronary blood flow that follows the intravenous administration of dipyridamole, was inversely related to wall stress. He therefore concluded that the level of systolic wall stress, and by inference the degree of wall thickness, plays the predominate role in regulating myocardial oxygen utilization in the diseased heart.

Myocardial oxygen supply and coronary blood flow in coronary artery disease: In the third paper of this Seminar, Neill and Fluri-Lundeen[13] review the problem of myocardial oxygen supply and subendocardial blood flow in the chronically overworked heart and the heart with obstructive coronary artery disease. In patients with aortic valve stenosis or incompetence the authors observed that both MVO_2 and coronary blood flow, when expressed per gram of myocardium, and wall stress were in the range expected for the normal heart. The increment in muscle mass and total coronary flow were proportional to systolic wall force, suggesting that the growth of muscle is regulated to maintain energy turnover, stress and blood supply. In patients with aortic stenosis myocardial lactate extraction was also normal, but only at rest; however, lactate production became evident when heart rate was elevated by pacing, a finding Neill and Fluri-Lundeen relate to a compromise in subendocardial perfusion. Evidence of anaerobic metabolism has likewise been elicited with pacing in patients with coronary artery disease and may also be the result of cell hypoxia and subendocardial ischemia.

Relation between cell anoxia and ventricular function after coronary occlusion: In the final paper, Harken and co-workers[14] report on their use of high speed reduced nicotinamide adenine dinucleotide (NADH) fluorescence to identify the temporal relation between cell anoxia and ventricular function after coronary occlusion in an isovolumetrically beating rabbit heart. The NADH fluorescence method provides an indication of intracell redox states in which the major component of the signal is derived from mitochondria. This technique is more specific for assessing oxygen deprivation than the traditional measurements of blood lactate and pyruvate and in addition provides a means for determining the distribution of anoxia. Areas of NADH fluorescence and cell anoxia were detected within 2 seconds after coronary occlusion. A significant reduction in developed systolic pressure and the derivation of pressure was noted within 6 seconds, suggesting that both the myocardial oxygen and oxidative reserves are negligible.

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The Metabolic Demand and Oxygen Supply of the Heart: Physiologic and Clinical Considerations

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The utilization of energy by the working heart has been studied extensively over the years. Because the conversion of chemical energy to mechanical work by the heart is highly dependent on oxygen, the oxygen required and the oxygen available for this conversion are considered to form the conceptual framework of the metabolic demand and supply of the heart, respectively. The oxygen requirement of the myocardium, as assessed by the rate of oxygen consumed ($M\dot{V}O_2$), is a function of the mechanical components of ventricular contraction and include: (1) the force developed and sustained by the muscular wall during its contraction; (2) the rate of force development; and (3) the frequency of generating force in the wall per unit time. The oxygen available to the mitochondria, which satisfies this requirement, is primarily determined by the oxygen delivered per unit of time (that is, coronary flow) and the oxygen extracted. Collectively, the response in flow and oxygen extraction represent the metabolic reserve of the heart.

Normally, during increments in work, coronary vascular resistance decreases permitting an increment in flow; oxygen extraction (65 to 70 percent) changes little under these circumstances. However, when the response in coronary vascular resistance is limited or at its optimal value, further increments in oxygen requirements are accompanied by an increase in oxygen extraction to 80 to 85 percent; oxygen extraction may exceed 90 percent in the presence of a reduced oxygen-carrying capacity. Stressed beyond the limits of its metabolic reserve (that is, minimum coronary vascular resistance and maximal oxygen extraction) the oxygen available to the heart becomes insufficient and, hence, an aerobic limit is reached. As a consequence, anaerobic metabolism commences, ventricular performance declines and pulsus alternans appear.

The concept of inappropriate oxygen demand relative to oxygen supply would appear to be central not only to the patient with coronary artery disease whose oxygen delivery may be compromised, but also to patients with chronic hemodynamic overload (for example, aortic stenosis) whose hypertrophied ventricle is now failing. Moreover, the implications of an aerobic limit may also explain the limits of hypertrophy.

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The energy requirements of the working heart have received much attention over the years. In the heart, unlike skeletal muscle, the conversion of chemical energy to mechanical work is highly dependent on oxidative reactions; an oxygen debt leads to a decline in ventricular performance. As a result the heart is considered to be an obligate aerobic organ.[1,2] The interrelation between oxygen requirements and oxygen availability, synonymous with the concept of metabolic demand and supply, is fundamental to any consideration of the heart's capacity for work. This is particularly the case for the ischemic heart whose oxygen availability, relative to oxygen requirements, may be compromised. In addition, it has been suggested that the metabolic demand of the mechanically

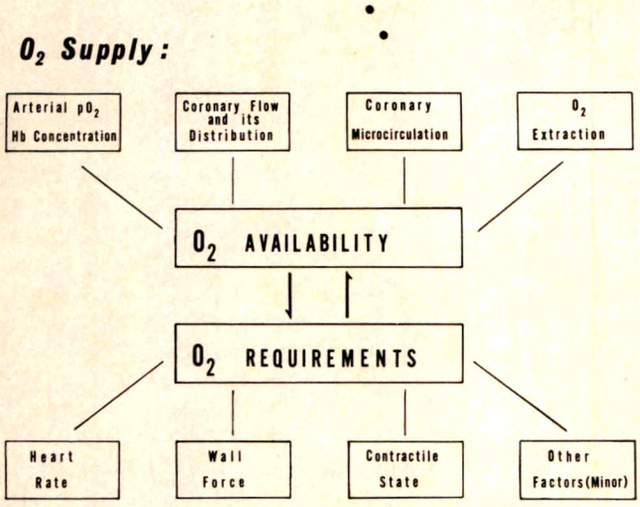

FIGURE 1. Schematic representation of the factors that regulate the demand and supply of oxygen in the heart cells and thereby reflect the heart's requirements for oxygen and its availability. Hb = hemoglobin.

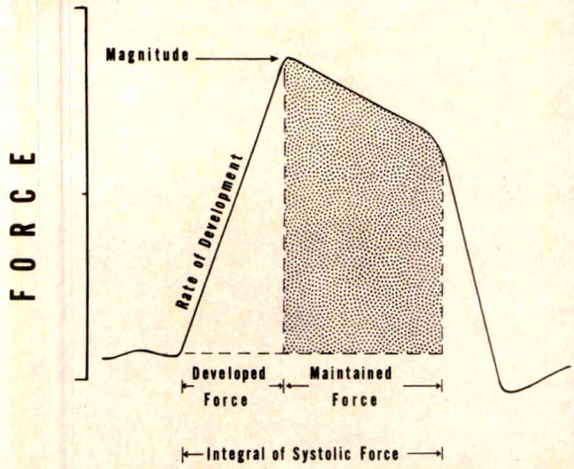

FIGURE 2. The major determinants of myocardial oxygen consumption expressed in relation to their influence on the components of systolic wall force.

overloaded heart (for example, aortic stenosis) eventually exceeds its available energy supply and, as a result, areas of hypoxia and subsequent fibrosis develop and the ventricle fails.[3,4] However, the actual role of hypoxia in the genesis and progression of the failing heart remains to be elucidated.

During the past 4 years we have been interested in examining those aspects of ventricular contraction that influence myocardial oxygen consumption (that is, the demand for oxygen[5,6] and those factors that regulate the availability of oxygen).[6,7] Moreover, we wanted to determine whether a limit to oxygen availability exists and what influence exceeding such an aerobic limit would have on ventricular performance.[7] This report reviews the physiologic principles that relate to the metabolic demand and oxygen supply in the heart and considers their relation to the pathophysiology of the diseased heart.

The Metabolic Demand of the Heart

Determinants of myocardial oxygen consumption: As an obligate aerobic organ the consumption of oxygen by the heart reflects its energy requirements. The energy utilized in maintaining organelle systems, the oxygen cost of electric depolarization and the activation of the contractile process have all been found to require only a minor fraction of the total energy consumed.[1,2] The major determinants of myocardial oxygen consumption ($M\dot{V}O_2$) (Fig. 1) include systolic wall force (as determined by chamber pressure and volume), myocardial contractile state and heart rate.[1,2] Hence, these components of ventricular contraction collectively represent the metabolic demand placed on the heart.

The relative contribution of each of the major determinants on $M\dot{V}O_2$ has been difficult to discern because they are interrelated through wall force. For example, alterations in contractile state or heart rate will influence both $M\dot{V}O_2$ and wall force. However, a uniform expression of energy utilization can be developed if the effects of a perturbation in contractile state and heart rate are related to $M\dot{V}O_2$ through their influence on the following components of wall force (Fig. 2 and Table I): (1) the magnitude of developed force; (2) the interval during which force is generated and maintained per contraction (that is, the integral of systolic force); (3) the rate of force development; and (4) the frequency with which force is developed per unit of time.

Wall force and the role of chamber pressure and volume: An increment in ventricular chamber pressure or volume would be expected to raise both the magnitude of force, which the myocardium and its fibers must

TABLE I

Factors Regulating the Components of Wall Force

Wall Force	Chamber		Contractile State		Heart Rate	
	Increased Pressure	Increased Volume	Increase	Decrease	Increase	Decrease
1. Magnitude	+	+	+ or −	+	0	0
2. Integral	+	+	−	+	−	+
3. Rate of development	+	+	+	−	+	−
4. Frequency of development	0	0	0	0	+	−

+ = increase, − = decrease; 0 = no change.

develop, and the force that is sustained during ejection (that is, the afterload). Hence, the total integral of systolic force for any given cardiac cycle is increased.[5] Increments in filling volume and diastolic pressure, which collectively reflect an elevation in preload and the degree of fiber stretch, would also raise the rate with which force is developed during the isovolumic contraction period. A reduction in diastolic chamber size, however, would reduce both the integral of systolic force and the rate of force development.

Role of myocardial contractility: The performance or output of either ventricle as a muscular pump is a function of the shortening of its constituent muscle fibers. Fiber shortening is determined by: (1) the load resisting its shortening (that is, afterload); (2) the length of the fiber during shortening; and (3) the contractile state of the fiber. Contractile state refers to that property of cardiac muscle that is independent of afterload or shortening length. For a more detailed discussion of cardiac mechanics the interested reader is referred to our recent review.[8]

Alterations in myocardial contractile state exert a predominant influence on the rate of force development and may also influence the magnitude of developed force[6] (*Table I*). The direction of these responses will be related to whether a positive or negative shift in contractility has occurred and whether this was induced pharmacologically by an agent that also has chronotropic properties or an influence on the resistance vessels (that is, arterioles) of the peripheral circulation. As a case in point, epinephrine would not only raise the inherent rate of force development, but also the frequency of force development per minute (that is, heart rate). The responses in the magnitude and integral of force after administration of epinephrine would also be influenced by the degree of arteriolar constriction. Hence, the overall effect of epinephrine would be an increment in $M\dot{V}O_2$.

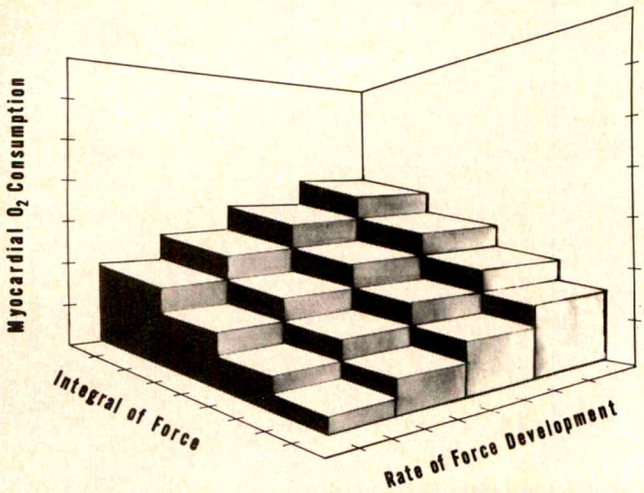

FIGURE 3. Three dimensional representation of the interrelations among myocardial oxygen consumption (cc/min per 100 g), the integral of systolic wall force per minute and the peak rate of force development.

Role of heart rate: Increments in the frequency of contraction result in an augmentation in net $M\dot{V}O_2$ expressed as cubic centimeters of oxygen consumed per minute. Because of the force-treppe phenomenon an augmentation in contractile state and the rate of force development also occurs.[6] However, under the circumstances the integral of systolic force may actually decline. As a result, the net energy utilization per beat will be dependent on the magnitude of these discordant responses.[6] For example, if an increment in heart rate raises the rate of force development less than the accompanying decline in the integral of force then the $M\dot{V}O_2$ per beat is actually reduced. Nevertheless, because the heart must generate and sustain a given force more frequently per unit of time with the tachycardia, the $M\dot{V}O_2$ per minute and force integral per minute are increased.

The interrelation between $M\dot{V}O_2$, the integral of force per minute (that is, reflecting the magnitude and duration of force and the influence of heart rate), and the rate of force development (that is, the role of contractile state) is shown in Figure 3. An increment in any of these components of wall force requires an almost equivalent elevation in energy expenditure. Hence, we chose to conceptualize the major determinants of $M\dot{V}O_2$ as follows: $M\dot{V}O_2 = a\text{TFI} + b\text{dF/dt} + c$, where TFI is the systolic force integral per minute, dF/dt is the peak rate of force development, c represents the minor determinants of oxygen consumption, and a and b are constants. Returning to the question of the relative cost of each of the major determinants, we have concluded[6] that for equivalent increments in force, whether achieved by raising diastolic volume or contractility, the augmentation in $M\dot{V}O_2$ is approximately the same; increments in heart rate, however, require a much larger expenditure of energy.

Reducing myocardial oxygen consumption: The response in the components of force, often proceeding in opposite directions, determine the clinical response to various therapeutic interventions. For example, patients with nocturnal angina, symptomatic heart failure and cardiomegaly may experience relief of their angina after digitalization. Conversely, patients with ischemic heart disease and normal heart size have an exaggeration of their anginal symptoms with digitalis. The explanation for these diametrically opposed results resides in the net effect of digitalis on force and thereby $M\dot{V}O_2$. In the presence of cardiomegaly digitalis diminishes chamber size and the magnitude and integral of force; it simultaneously will also raise the rate of force development. In those patients whose angina is relieved after digitalis, the net result is a decline in $M\dot{V}O_2$, which is explained by the decrease in the force integral being greater than the accompanying increase in the derivative of force. However, the extent to which chamber dimension can decline in the normal-sized heart after digitalis is limited and, as a result, the increment in the rate of force development is unopposed, leading to an imbalance in oxygen demand and supply and consequently angina. These discordant responses in force and hence $M\dot{V}O_2$ after digitalis have also been demonstrated

in the experimental animal.[9] A reduction in intravascular and intracardiac volume with diuretic agents would also be expected to lower the energy requirements of the enlarged and failing heart.

Propranolol and nitrates represent the mainstay in the treatment of patients with angina. Viewed simplistically, propranolol decreases $M\dot{V}O_2$ by reducing heart rate and the rate of force development. Nitrates, such as isosorbide dinitrate, are able to reduce metabolic demand by peripheral venodilatation, which attenuates the venous return and chamber dimension throughout the cardiac cycle. Hence, the magnitude and rate of force development decline with nitrates. The response in heart rate and blood pressure (that is, the double product) to propranolol and nitrates provides a useful clinical estimate of the reduction in $M\dot{V}O_2$.

Metabolic Supply of the Heart

Concept of metabolic reserve: The capacity of the heart for work, unlike that of skeletal muscle, is greatly dependent on aerobic conditions. The amount of oxygen available to the myocardium (Fig. 1) and its mitochondria, in particular, is determined by (1) the arterial oxygen content and hemoglobin concentration (that is, oxygen-carrying capacity); (2) coronary flow and its distribution through the microcirculatory network (that is, oxygen delivery); (3) the anatomic characteristics of the coronary microcirculation, including the relation of capillaries to myocardial fibers and the diffusion distance for oxygen; and (4) the portion of this delivered oxygen that is driven from the capillaries into the intracellular compartment and which also reflects the influence of transit time. Within the cell, the diffusion of oxygen to the mitochondria is facilitated by the reversible combination of myoglobin with oxygen and the translational diffusion of oxymyoglobin.[10] During acute increments in work the myoglobin content, mitochondrial oxygen tension, and capillary oxygen tension remain unchanged while coronary flow increases. *This increment in coronary flow has been attributed to two possible mechanisms that reflect the adaptation of the microcirculation to variations in metabolic demand.* The first involves a redistribution of flow from nonexchanging to exchanging vessels[11] in a manner analogous to the concept of ventilation:perfusion ratios in the lung. The other mechanism focuses on a recruitment in the number of perfused channels, or the density of open capillaries.[12] However, the relative contribution of either mechanism, remains uncertain. Oxygen extraction may also increase with an augmented work load, but to a lesser extent than the elevation in flow. In the chronically overloaded hypertrophied heart it is not clear whether a proliferation of the capillary bed occurs,[3] thereby preserving the normal diffusion distance for oxygen between the hypertrophied fiber and its capillary bed, or whether part of the adaptation process involves myoglobin or mitochondrial energetics. Nonetheless we have viewed the compensatory adjustments in both flow and oxygen extraction, which occur during acute or chronic elevations in work, as constituting the *metabolic reserve* of the heart.

Capillary oxygen delivery is established by coronary blood flow, coronary arterial oxygen content, and the oxygen-carrying capacity (that is, hemoglobin concentration). For any given hemoglobin level the amount of delivered oxygen (coronary flow × arterial oxygen content) that is actually consumed (that is, coronary flow × arteriovenous oxygen difference) represents the oxygen extracted or, more simply, the ratio of the arteriovenous oxygen difference to the arterial oxygen content. Unfortunately, these measurements do not actually establish the adequacy of the delivered oxygen relative to the mitochondrial oxygen content; rather, they only approximate the kinetics of intracellular molecular oxygen. However, either lactate and pyruvate, or the ratio of reduced to oxidized nicotinamide adenine dinucleotide (NADH/NAD) would reflect the proportion of reduced to oxidized substrate and thereby provide a better description of the adequacy of oxygen delivery to the intracellular compartment. Lactate and pyruvate measurements have been used for this purpose for some time. However, the measurement of NADH using a fluorescence photographic method represents a more recent technique that is now available for this purpose.[13] Harken et al.[14] discuss the relation of NADH to ventricular performance after coronary occlusion in this Seminar. Their findings suggest that myocardial oxidative reserve is negligible.

Reserve in oxygen extraction: For a wide variety of conditions, including exercise,[15,16] atrial pacing,[17] catecholamine infusion,[18,19] hyperthyroidism[20] and various cardiac diseases,[15–19,21–24] myocardial oxygen extraction has been found to range between 65 and 75 percent. It has often been presumed that oxygen extraction is invariant and that the 65 to 75 percent range represents a physiologic limit. However, this may not be the case when coronary flow is restricted. Daniell[25] has observed that in the open chest dog, myocardial oxygen extraction reaches a maximal value of 84 ± 3 percent, with progressive reductions in total left coronary flow. Shea et al.[26] reported a similar plateau in oxygen extraction when left coronary flow was limited in the open chest dog. Case et al.[27] observed that when coronary flow was not controlled during progressive reductions in hematocrit, oxygen extraction was invariant as work was increased. However, when coronary stenosis was superimposed in two hearts during similar conditions of anemia and work, oxygen extraction increased to 85 and 91 percent, respectively.[7] Our findings on oxygen extraction and its maximal limit are in close agreement with these observations. Using an isolated canine heart preparation in which coronary flow and oxygen extraction could be measured continuously during progressive increments in metabolic demand, we observed that oxygen extraction will plateau at approximately 82 percent in either the normally perfused or panischemic heart. When the oxygen-carrying capacity had been reduced by producing a dilutional anemia, oxygen extraction exceeded 90 percent. Moreover, our observations in the underperfused heart indicated that myocardial ischemia and hypoxia are not synonymous. Hypoxia, as evidenced by the onset of

myocardial lactate production, does not occur until the conditions of oxygen availability are exceeded.

The fundamental issue pertaining to maximal oxygen extraction, therefore, is the relation between the demand for oxygen and the available oxygen supply. Although a large fraction of the delivered oxygen (65 to 75 percent) is utilized by the heart under a variety of circumstances, oxygen extraction is not maximal unless the coronary vascular reserve has been fully utilized (that is, optimal vasodilatation) or the oxygen-carrying capacity of blood is compromised in the coronary flow-limited heart. This reserve in oxygen extraction has been schematically represented in Figure 4.

Observations in patients with coronary artery disease would appear to indicate a similar response; however, variations in regional flow and segmental obstructive coronary disease differing in severity and location preclude direct comparisons with the panischemic canine heart. Messer et al.[21] found that 23 of 28 patients with coronary artery disease increased their oxygen extraction during exercise from an average of 69 percent at rest to 75 percent after 7 minutes of exercise; 91 percent of patients without coronary artery disease had no change in oxygen extraction (70 ± 6 percent) during similar levels of work. In the series of Cohen et al.,[22] 13 of 38 patients with coronary artery disease did not experience an increase in coronary flow during the intravenous administration of isoproterenol. In 6 of these 13 patients myocardial oxygen extraction was increased or unchanged, as opposed to the response in normal subjects, whose coronary flow increased 65 percent and oxygen extraction decreased from 72 to 66 percent during isoproterenol infusion.[17] Neill[23] found that during atrial pacing coronary arteriovenous oxygen difference remained unchanged in two patients and increased in four patients with coronary disease. Angina developed in all six of these patients.

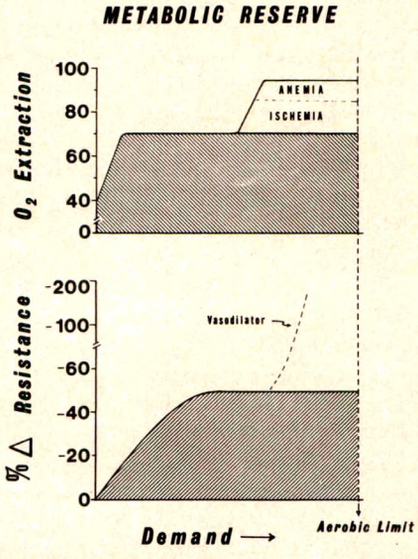

FIGURE 4. The metabolic reserve of the heart may be described by the changes in oxygen extraction (percent) and the percent decrease in coronary vascular resistance that occur in response to a progressive elevation in metabolic demand. Note that oxygen extraction reaches a plateau early and does not increase again until the coronary vascular reserve has reached its optimal level. Myocardial ischemia or anemia will promote a greater extraction of oxygen. Coronary vasodilators, such as dipyridamole, may increase coronary flow beyond its optimal limits. Once oxygen extraction and coronary flow are maximal, additional increments in demand result in cell hypoxia and, thus, the aerobic limit of the heart is exceeded.

Coronary vascular reserve: Utilization of the reserve in oxygen extraction represents a minor response to increments in aerobic work and demand and is brought into play only under conditions in which oxygen delivery is impaired. The coronary vascular reserve, or density of open capillaries, represents the major compensatory response to increased oxygen needs. The importance of alterations in coronary flow has been amply demonstrated during increments in oxygen demand created by exercise[15,16] or atrial pacing[17] or when the oxygen-carrying capacity[7,27] or arterial oxygen tension[28] was purposely reduced.

We examined the boundaries to the coronary vascular resistance (that is, the ratio of the pressure gradient across the coronary circulation to coronary flow), which accompanies coronary vasodilatation during marked increments in aerobic work. It was observed[7] that for conditions in which coronary perfusion pressure was held constant (80 mm Hg) coronary flow increased by an average amount of 45 percent (range 35 to 63 percent). Coronary vascular resistance, therefore, decreased to a similar degree. These findings are in accord with those of others in experimental animals[26,27] and man[15,18–19] in which a variety of conditions were imposed on the myocardium and thereby the coronary circulation. Hence, a substantial decline in coronary vascular resistance occurs during increments in aerobic demand, which permits an increased delivery of oxygen (Fig. 4). This decline in coronary vascular resistance represents the optimal coronary vasodilatation that results for the given metabolic demand. However, coronary flow is not maximal. We have found that flow may increase even further under these conditions when dipyridamole, a potent coronary vasodilator, is administered.[7] However, despite the fact that coronary flow has increased with dipyridamole, ventricular performance (that is, the developed force-length relation) was noted to decline, suggesting that a nonpreferential redistribution of regional coronary flow (that is, "a coronary steal") has been created.

This unexpected response in flow when coronary vasodilatation was at its presumed maximum suggests that the coronary vascular resistance is reduced in a heterogeneous fashion during increments in metabolic demand and that this adjustment in resistance is based on the given relation between supply and demand in various regions of the myocardium. Coronary vascular resistance, therefore, achieves an optimal, albeit not maximal level during increments in aerobic work. The explanation for the response in resistance, related to presumably heterogenous differences in demand, remains to be elucidated.

Aerobic limit of the heart: When the metabolic reserve of the heart is fully utilized (that is, maximal oxygen extraction and optimal vasodilatation) any further demand for oxygen cannot be satisfied. We have viewed this state as representing the aerobic limit of the heart. Beyond this aerobic limit additional increments in oxygen requirements result in metabolic demand exceeding the oxygen supply and, hence, cellular hypoxia. As a result anaerobic metabolism commences and intracellular oxidation-reduction systems shift to a more reduced state. Lactate accumulates intra- and extracellularly as reflected by a decrease or reversal in the arterial-coronary sinus lactate difference, lactate extraction and the production of lactate.[29] These measurements have been utilized for some time as an indication that the aerobic limit has been surpassed and also to assess the adequacy of coronary flow and oxygen availability in both human being[16–18,20,22–24,30,31] and experimental animal.[7,26,27]

Shea et al.[26] found a net lactate production across the myocardium when coronary flow was reduced from 160 to 35 ml/min. At this juncture of negative arteriovenous lactate difference, oxygen extraction was more than 78 percent. These investigators examined the influence of increments in pressure work when coronary flow was held constant. Here again, atrioventricular lactate difference became negative when coronary vascular resistance had reached its minimal value. In our studies[7] anaerobic metabolism also occurred when the metabolic demand exceeded the available supply of oxygen. This imbalance in demand and supply could be produced in either the normally perfused or panischemic heart. It is clear that left ventricular performance decreased when the aerobic limit was surpassed. Pulsus alternans appeared in the majority (more 80 percent) of hearts irrespective of the coronary perfusion pressure.[7] The appearance of pulsus alternans in hearts perfused at 80 mm Hg suggests that an imbalance in supply and demand might also exist in the failing, nonischemic heart and that these hearts may "outdistance" their blood supply.

Myocardial Energy Utilization in Acquired Heart Disease

Conditions of imbalanced supply and demand: Fallen et al.[18] examined the response in coronary flow, oxygen extraction and lactate metabolism to an isoproterenol infusion in patients with aortic valvular stenosis and angina. In five patients having angina without coronary artery disease, the isoproterenol challenge was not accompanied by the expected normal rise in coronary flow. However, oxygen extraction did increase in three of these patients, and myocardial lactate production developed in all five patients. In seven patients with aortic stenosis without angina, coronary flow increased significantly (47 percent), oxygen extraction decreased and only one patient had any evidence of myocardial glycolysis, although it was uncertain whether or not this patient had normal coronary arteries. Myocardial lactate production has also been observed in patients with aortic stenosis by Trenouth, et al.[17] when heart rate was raised to 120 to 140 beats/min by atrial pacing; lactate extraction became negative in 6 of these 12 patients. All six of these patients had a history of exertional angina despite the absence of coronary artery disease. The 12 patients with aortic stenosis all underwent surgical replacement of their diseased valve. Of the four patients who did not survive operation or died within 3 months of their operation, three had demonstrated negative lactate extraction (mean −31 percent) during atrial pacing.

In the series of Cohen et al.,[22] 38 patients with coronary artery disease had metabolic studies during an isoproterenol challenge. Thirteen of these patients did not have a significant increase in coronary flow; 6 of these 13 had either no change or an increase in oxygen extraction, whereas in 5 of these 6 patients lactate extraction declined to less than 10 percent or became negative. Neill[23] also examined the response in myocardial metabolism in 13 patients with coronary artery disease and angina. Here oxygen demand was raised by atrial pacing. During the tachycardia (120 to 140 beats/min), coronary arterieovenous lactate difference became negative in three patients and the oxygen difference and percent extraction increased in two of these three patients. One other patient whose lactate extraction was negative before pacing had an even further decline in the arteriovenous lactate with tachycardia. Hence, in four patients it was possible to demonstrate that the demand for oxygen exceeded the available supply. The fact that these findings could not be demonstrated in the remaining patients may merely reflect the limitations of the coronary sinus sampling site as an index of regional differences in coronary flow and demand in segmental coronary artery disease.

Oxygen availability and heart failure: Over the years several schools of thought have developed regarding those events that initiate failure. One theory that has received recent support emphasizes a feedback control of ventricular hypertrophy based on normalizing wall force per unit of muscle (that is, wall stress).[32] Hypertrophy, which may have served for many years to normalize the augmented wall force of the pressure- or volume-overloaded heart, eventually becomes incapable of compensating for the increased hemodynamic load. Hence, failure results, accompanied by a continuing cycle of progressive chamber enlargement and failure. The explanation for this inappropriate response in wall thickness, and presumably protein synthesis, is unknown. Other investigators[3] have theorized that the metabolic demand of the mechanically overburdened heart eventually exceeds its available energy supply. As a consequence, a defect in mechanical performance and protein synthesis ensues. It is these events that lead to progressive chamber dilation and inappropriate elevation in wall stress without concomitant hypertrophy.

Most clinical studies in patients with cardiac disease have observed a common range for coronary flow and $M\dot{V}O_2$ when expressed per 100 g of ventricle.[15–18,20,23,24,30,33–36] This range corresponds to that

TABLE II

Ventricular Mass and Energetics in Aortic Stenosis

	Normal Heart	→	Compensated AS	→	Decompensated AS
Peak systolic wall force (g)	2,835		8,160		13,060
End-diastolic volume (cc)	100		125		250
LV pressure (mm Hg)	80		200		200
LV mass (g)	125		450		600
Peak systolic wall stress	152		146		216
$M\dot{V}O_2$ (cc/min)	10		36		48
Coronary blood flow (cc/min)	100		360		480
O_2 extraction (%)	75		75		80
$M\dot{V}O_2$ (cc/min per 100 g)	8		8		8
Coronary blood flow (cc/min per 100 g)	80		80		80

AS = aortic valve stenosis; LV pressure = left ventricular pressure at aortic valve opening, which approximates the point of peak systolic wall force; $M\dot{V}O_2$ = myocardial O_2 consumption; Normal heart = trivial to nonexistent aortic valve gradient.

observed in patients without significant cardiac disease. Because of the increased muscle mass with cardiac disease, total coronary flow and $M\dot{V}O_2$ are substantially increased. Comparison of $M\dot{V}O_2$ in patients at rest with compensated and decompensated failure has also revealed no differences even though the wall stress was shown to be greater in the patient with symptomatic failure. However, as discussed earlier in this review, when metabolic demand is raised in patients with heart failure, as occurs with pacing or isoproterenol administration, evidence of cell hypoxia results and myocardial lactate is produced despite the absence of obstructive coronary disease. This response suggests that under these circumstances metabolic demand exceeds the given metabolic supply. Considering that the total coronary flow (expressed in cc/min) may be increased three to four times above normal, commensurate with the increase in muscle mass, it is not surprising that the coronary vascular reserve may be fully utilized under these circumstances.

The response in ventricular mass and energetics that occurs as a result of an augmented hemodynamic load may be described in the following manner (Table II): In aortic valve stenosis, for example, the gradual narrowing of the valve orifice imposes a progressive hemodynamic burden on the ventricle. Consequently, wall force and $M\dot{V}O_2$ (cc/min) are increased and myocardial mass begins to increase. Once a stable phase of hypertrophy results, the energy utilization per cell (and mass) is again normal; force is now also distributed over a greater surface area of fibers and, hence, wall stress (force per cross-sectional area of muscle) returns to the expected normal range (the compensated phase).[32] Eventually, coronary flow, or specifically capillary vasodilatation, and oxygen extraction reach their optimal limit and exhaust the *metabolic reserve.* Under these circumstances the supply of oxygen to the heart may prove adequate only at rest. During conditions in which oxygen demand is raised, anaerobic metabolism occurs. As a result of the cell hypoxia a decline in contractile state follows and the heart fails, leading to a further increment in chamber size and, as a consequence, a progressive elevation in wall force. At this point (decompensated phase) metabolic demand, as determined by systolic force, is greater than the supply of energy and, as a result, protein synthesis and myocardial mass cannot keep pace with the existing needs. Consequently, wall stress is also increased. Oxygen utilization would likewise be raised and to a level that is dependent on the absolute increment in force. A vicious cycle of progressive increments in demand ensues, which is unaccompanied by compensatory alteration in myocardial growth.

The correction of the disease state at this point may or may not ameliorate the demand. The response in demand would seemingly be a function of the response in wall force. If demand is attenuated and the balance between supply and demand is restored, then the depression in contractility may be reversed. In this case, mass would also gradually regress to more normal levels. If it were possible to document routinely the metabolic reserve and an imbalance in supply and demand in the overloaded heart with such interventions as pacing or catecholamine infusion, this information might prove useful in assessing the degree of failure, the timing of operative intervention and the utility of the compensatory response in mass. However, the validation of this argument requires systematic study. Finally, the problem of oxygen availability may represent just one of many mechanisms that may be deranged in the failing heart.

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Myocardial Oxygen Consumption in Chronic Heart Disease: Role of Wall Stress, Hypertrophy and Coronary Reserve

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The relations between left ventricular mass, mass to volume ratio, systolic wall stress and myocardial oxygen consumption were analyzed in 187 patients with chronic heart disease. The degree of left ventricular hypertrophy is determined by mass, the mass to volume ratio, and pressure and, hence, systolic wall stress. For each condition an inverse relation exists between mass to volume ratio and peak systolic wall stress. In chronic heart disease at least two types of inappropriate left ventricular hypertrophy may occur: (1) low stress hypertrophy with an increased mass to volume ratio, normal left ventricular function and normal or reduced oxygen consumption ($M\dot{V}O_2$), whereas (2) high stress hypertrophy has a normal or low mass to volume ratio, impaired left ventricular function and an increased $M\dot{V}O_2$. The range of systolic wall stress was 100 to 450 $\times 10^3$ dynes/cm^2 and reflects the stress that could be altered by inotropic interventions and changes in systolic pressure. A similar reserve capacity is present for both the metabolic and the coronary reserves. Total left ventricular oxygen consumption is related to total left ventricular mass. This relation is influenced by the degree of viability of left ventricular mass, by the mass to volume ratio and by inotropic interventions. Left ventricular oxygen consumption per viable mass unit ($M\dot{V}O_2$) is significantly correlated with the systolic force per unit cross-sectional area of the left ventricular wall, that is, to left ventricular systolic wall stress.

It is concluded that peak systolic wall stress represents one of the major determinants of myocardial oxygen consumption and of ventricular performance. It closely relates to the appropriateness of left ventricular hypertrophy, which may be defined by the relation between systolic pressure, mass to volume ratio and peak systolic wall stress.

The oxygen consumption (MVO_2) of the human heart is determined by many factors, mainly by systolic tension development or stress, heart rate and contractility.[1–3] Of lesser importance to the overall $M\dot{V}O_2$ are the oxygen costs associated with shortening and the basal or resting metabolism.[1] These determinants of $M\dot{V}O_2$ are valid for the healthy state, for acute hemodynamic or inotropic interventions and for chronic hypertrophy and failure. However, it remains to be elucidated to what extent the degree and appropriateness of ventricular hypertrophy or dilatation, or both, may influence and modify the relations between $M\dot{V}O_2$ and its classic determinants in man. This study was therefore aimed at evaluating the role of ventricular mass, volume, mass to volume ratio and wall stress on the oxygen demand of the human left ventricular myocardium in various clinical conditions. The results indicate that systolic wall stress, as a consequence of the degree of ventricular hypertrophy, plays the predominant role in ventricular function and myocardial overall energy demand in chronic heart disease.

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TABLE I

Comparative Data in Normal Subjects and Patients

	Cases (no.)	EF	LVMM	LVMM/EDV	T_{syst}	$M\dot{V}O_2$	$L\dot{V}O_2$
Normal subjects	12	72 ± 2	92 ± 6	1.21 ± 0.12	220 ± 9	7.98 ± 0.52	13.3 ± 2.1
CAD	36	52 ± 11	145 ± 22‡	1.12 ± 0.16	236 ± 18	7.9 ± 0.39	20.6 ± 3.2
SVD	8	69 ± 8	84 ± 14	1.18 ± 0.21	206 ± 22	6.4 ± 0.6‡	9.7 ± 0.91‡
AS*	6	74 ± 4	145 ± 10§	2.1 ± 0.31	192 ± 23	8.1 ± 0.8	21.1 ± 2.3§
AS†	9	46 ± 11	190 ± 17‖	1.01 ± 0.11	396 ± 95§	14.9 ± 1.6‖	51.0 ± 6.9‖
AI	12	58 ± 7	174 ± 22‖	1.12 ± 0.13	329 ± 36‡	14.2 ± 1.4‖	45.4 ± 4.7‖
HOC	12	78 ± 6	~228	~3.78	142 ± 52‡	8.6 ± 1.21	35.3 ± 3.6
EH	92	62 ± 6	152 ± 12‖	1.52 ± 0.33	266 ± 18§	10.7 ± 0.38‖	29.3 ± 4.1‖

* Clinically compensated (New York Heart Association classes I and II), concentric hypertrophy.

† Clinically compensated (New York Heart Association Class III and IV), LV dilatation.

‡ $P < 0.05$.

§ $P < 0.01$.

‖ $P < 0.001$.

AI = aortic incompetence; AS = aortic stenosis; CAD = coronary artery disease; EF = ejection fraction (%); EH = essential hypertension; HOC = hypertrophic obstructive cardiomyopathy; LVMM = left ventricular muscle mass (g/m^2); LVMM/EDV = left ventricular muscle mass to volume ratio (g/ml); $L\dot{V}O_2$ = total left ventricular oxygen consumption (ml/min); $M\dot{V}O_2$ = myocardial oxygen consumption per weight unit (ml/min × 100 g); SVD = small vessel disease; T_{syst} = peak circumferential systolic wall stress (10^3 dynes/cm^2).

Methods

Patients: Studies were carried out from 1969 to 1978 in a total of 187 patients (Table I). At the time of diagnostic cardiac catheterization, left ventriculography and coronary blood flow measurements were performed. Patients were grouped accordingly: 12 subjects without cardiovascular disease (normal group), 36 patients with coronary artery disease, 8 patients with coronary vasculitis (small vessel disease) on the basis of systemic immune complex vasculitis (4 cases) and coronary involvement in systemic lupus erythematosus (4 cases), 15 patients with aortic stenosis either in New York Heart Association functional class[4] I or II (6 cases) or class III or IV (9 cases), 12 patients with aortic incompetence (all in functional class III or IV), 12 patients with hypertrophic obstructive cardiomyopathy and 92 patients with hypertensive heart disease due to essential hypertension. The latter group, on the basis of ventriculographic findings and coronary angiography, was classified into four subgroups: group I, compensated essential hypertension (functional class I) without coronary artery disease; group II, compensated essential hypertension (functional class I) with 75 percent or greater stenosis of the left anterior descending coronary artery without regional wall contraction abnormalities; group III, essential hypertension with regional wall motion abnormalities (hypokinesia and akinesia) due to coronary artery disease; and group IV, decompensated essential hypertension (functional class IV) on the basis of global wall contraction abnormalities (Table II).

TABLE II

Comparative Data in Normal Subjects and Patients With Hypertensive Hypertrophy (Groups I to IV)

	$\bar{P}_{art}$	LVMM	LVMM/EDV	dP/dt_{max}	T_{syst}	$M\dot{V}O_2$
Normal subjects	91 ±9	92 ±6	1.21	1690 ±90	220 ±9	7.98 ±0.52
I*	136 ±9**	122 ±11¶	1.65	2460 ±110**	232 ±8	8.21 ±0.31
II†	128 ±6**	129 ±14#	1.61	2400 ± 94**	208 ±19	7.13 ±0.19
III‡	131 ±3**	168 ±16**	1.50	2310 ±88#	256 ±18	9.62 ±0.34¶
IV§	146 ±4**	192 ±15**	1.31	2190 ±102¶	369 ±26**	12.8 ±0.61#

* Essential hypertension without coronary artery disease.

† Essential hypertension with coronary artery disease.

‡ Essential hypertension with regional wall motion abnormalities.

§ Decompensated essential hypertension (functional classes III and IV).

‖ $P < 0.05$.

¶ $P < 0.01$.

# $P < 0.005$.

** $P < 0.001$.

CI = cardiac index (liters/min per m^2); dP/dt_{max} = maximal rise of left ventricular pressure development (mm Hg/sec); EF = ejection fraction (%); LVMM = left ventricular muscle mass (g/m^2); LVMM/EDV = left ventricular muscle mass to volume ratio (g/ml); $M\dot{V}O_2$ = myocardial oxygen consumption per weight unit (ml/min × 100g); P_{art} = mean arterial pressure (mm Hg); T_{syst} = peak circumferential systolic wall stress (10^3 dynes/cm^2); V_{CF} = mean circumferential fiber shortening (circumferences/sec).

Cardiac catheterization and angiography: Left ventricular and aortic pressures were measured through catheters (pigtail, Cordis) that were directly connected to pressure transducers (Statham F23 Gb). The catheter system had a natural frequency above 20 hertz and a phase lag linear with frequency in this frequency range.

Left ventriculograms were obtained with multiple hole catheters using power injections (Contrac) and 40 to 60 ml of 76 percent meglumine sodium diatrizoate. The projection was 30° in the right anterior oblique view.[5–8] Left ventricular volumes were calculated with the methods of Greene et al.[5]: $V = \pi\ LM^2/6$ (V = volume, L = longest measured chamber axis and M = internal transverse diameter at the mid point of L). L was taken directly from the ventriculogram and M was derived from the area (F) of the left ventricle ($M = 4.F/\pi\ L$). In each patient the correction factor was determined considering magnification and distortion. Volume measurements were performed for end-diastole as well as for each frame during systole until the peak value of systolic circumferential wall stress was obtained.[7–12]

Peak systolic wall stress was determined from intraventricular pressure, radius and wall thickness with use of the Laplace equation ($T_{syst} = P.r/2d$) (P = peak systolic developed pressure, r = internal left ventricular radius and d = wall thickness). The left ventricular internal radius has been derived from volume measurements ($r = \sqrt[3]{3.V/4\pi}$). Wall thickness (d) was taken frame by frame as the averaged thickness of a 4 cm segment of the free wall on the anterior projection one third of the distance from the apex. Each value for (1) intraventricular pressure, (2) ventricular radius, and (3) ventricular wall thickness was taken for the instantaneous wall stress calculation until the peak value of systolic circumferential wall stress was obtained. The stress calculated by this procedure represents mean values across the thickness of the wall. This mean value underestimates maximal stress, which occurs at the endocardium, and it overestimates minimal stress at the outer layers (epicardium); however, application of the mean value does not lessen the validity of this stress value because it deviates from thin-walled calculations by approximately 10 percent.

Determinations of left ventricular mass were made from end-diastolic chamber dimensions, that is, from end-diastolic measurements of wall thickness and volume. These calculations were based on the determinations of shell volume created by adding lateral wall thickness to calculated ellipsoidal chamber dimensions and subtracting adjusted chamber volume. Shell volume was converted to mass by multiplying by the specific gravity of heart muscle: left ventricular muscle mass (LVMM) = LVTV − EDV (LVTV = left ventricular total volume; EDV = end-diastolic volume); $LVTV = 4/3{\cdot}\pi\ (L/2 + d)\ (M/2 + d)^2$; $LVMM = 4/3{\cdot}\pi\ (L/2 + d)\ (M/2 + d)^2 - EDV$. Left ventricular mass to volume ratio was obtained by dividing left ventricular mass by the end-diastolic volume.

Coronary sinus sampling and coronary blood flow: A Goodale-Lubin catheter (Ch. 7) was inserted through the left cubital vein and introduced into the coronary sinus for coronary sinus blood sampling and for coronary blood flow determinations. Coronary blood flow was measured after right and left heart catheterization and before left ventriculography by means of the argon method with gas chromatographic analysis of argon in arterial and coronary venous blood. Details as well as the accuracy of this method, which allows measurements of coronary blood flow up to 400 to 450 ml/min × 100 g, have previously been published in detail.[13–16] The linearity of this method over the whole range of physiologically

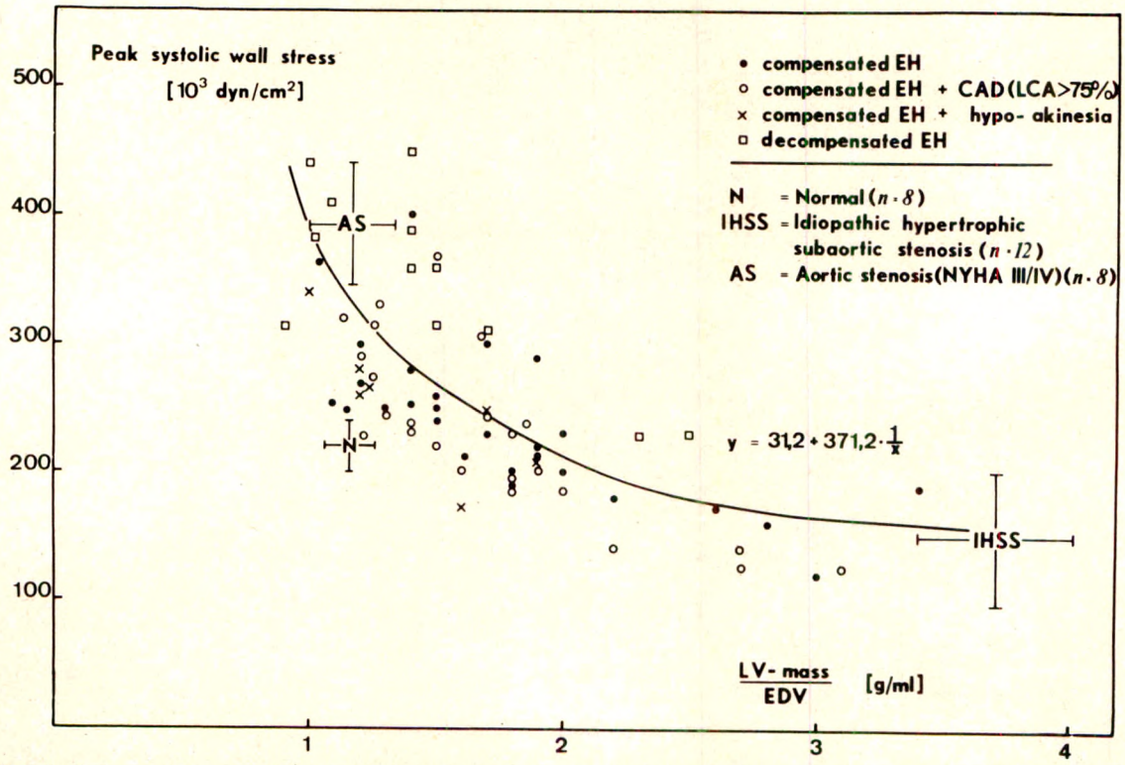

FIGURE 1. Relation between left ventricular mass to volume ratio (LV − mass/EDV) and peak systolic wall stress. Note the inverse relation and the position of patient groups with hypertrophic obstructive cardiomyopathy (IHSS) and aortic stenosis (AS), respectively. CAD = coronary artery disease; dyn = dynes; EH = essential hypertension; LCA = left coronary artery; N = normal subjects; NYHA = New York Heart Association functional class.

existing coronary blood flow was proved using comparisons with flowmeter and coronary sinus sampling techniques.[13,14] Argon blood concentrations were determined after extraction through a specially designed extraction chamber by gas chromatography (trace gas analyzer 1533 B, Varian, Darmstadt, FRG). Measurements of coronary blood flow were carried out under resting conditions and during maximal coronary vasodilation. The latter was achieved by the intravenous injection of a potent coronary vasodilator (dipyridamole 0.5 mg/kg), which was given to each patient in fractions appropriate to exert no major effects on aortic pressure or heart rate.[15] Coronary vascular resistance (mm Hg/ml per minute × 100 g) was determined as the ratio between mean diastolic aortic pressure minus mean left ventricular diastolic pressure and coronary blood flow.[15–18] Coronary vascular reserve, or coronary reserve, was defined as the ratio between coronary vascular resistance in the resting state and under maximal coronary vasodilation.[17] Left ventricular oxygen consumption (ml/min × 100 g) was determined as the product of coronary blood flow (ml/min × 100 g) and the arterial-coronary venous oxygen difference (volume percent). Arterial and coronary venous oxygen saturations were measured with carbon monoxide oximetry. Statistical analysis was performed with Student's *t* test.

Results

Appropriateness of left ventricular hypertrophy: In the patients with essential hypertension the mean arterial pressure was increased by 40 to 50 percent in comparison with the normal subjects. There was no significant difference in mean arterial pressure in the four hypertensive subgroups (Table II). In contrast, left ventricular mass was increased an average of 40 and 44 percent, respectively, in hypertension groups I and II, and 78 and 96 percent, respectively, in groups III and IV, despite a similar pressure load. The ratio of left ventricular mass to mean systolic pressure load was therefore greatly increased in groups III and IV (advanced hypertension). The mass to volume ratio was increased in groups I and II by 36 and 33 percent, respectively, and moved to normal values in patients with decompensated essential hypertrophy (group IV). The latter change was due to a larger increase in end-diastolic volume despite progressive mass augmentation. Therefore, the increase in left ventricular mass was not accompanied by a comparable increase in mass to volume ratio.

Peak circumferential systolic wall stress was normal in the groups I and II (essential hypertension), whereas it was considerably increased in groups III and IV (Table II). An inverse relation was present between mass to volume ratio and peak systolic wall stress, indicating a characteristic decrease in peak systolic wall stress with increase in the mass to volume ratio (Fig. 1). The largest mass to volume ratio was found in the patients with hypertrophic obstructive cardiomyopathy and the lowest values were present for decompensated subgroups with pressure and volume overload. Compensated left ventricular hypertrophy due to essential hypertension and aortic stenosis was within this hypertensive correlation, whereas in the normotensive patient groups there was a shift to lower peak systolic

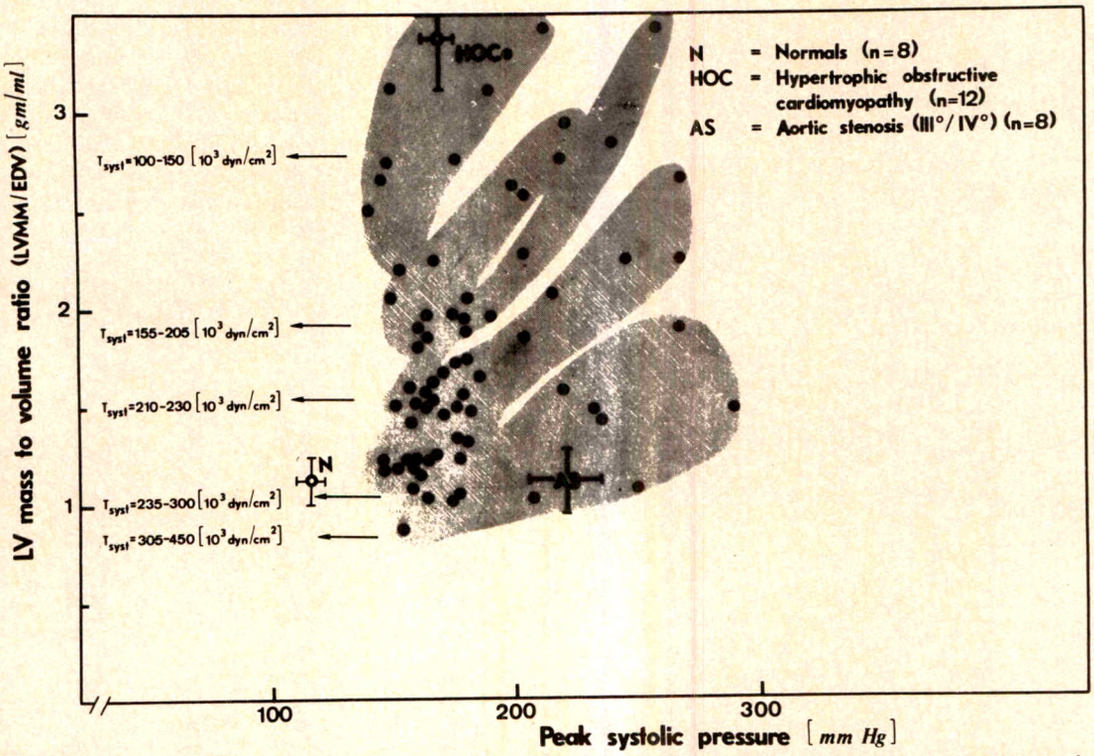

FIGURE 2. Relation between peak systolic pressure and left ventricular (LV) mass to volume ratio separated on the basis of nonoverlapping isostress ranges. At comparable systolic pressure, the peak systolic wall stress (T_{syst}) decreases with increase in mass to volume ratio. At comparable mass to volume ratio the peak systolic wall stress increases with increase in systolic pressure. However, peak systolic wall stress may remain normal even at an extreme increase in pressure, provided that the mass to volume ratio also increases in proportion to pressure load. **Closed circles** indicate patients with essential hypertension. III°, IV° = New York Heart Association functional classes III and IV; other abbreviations as in Figure 1.

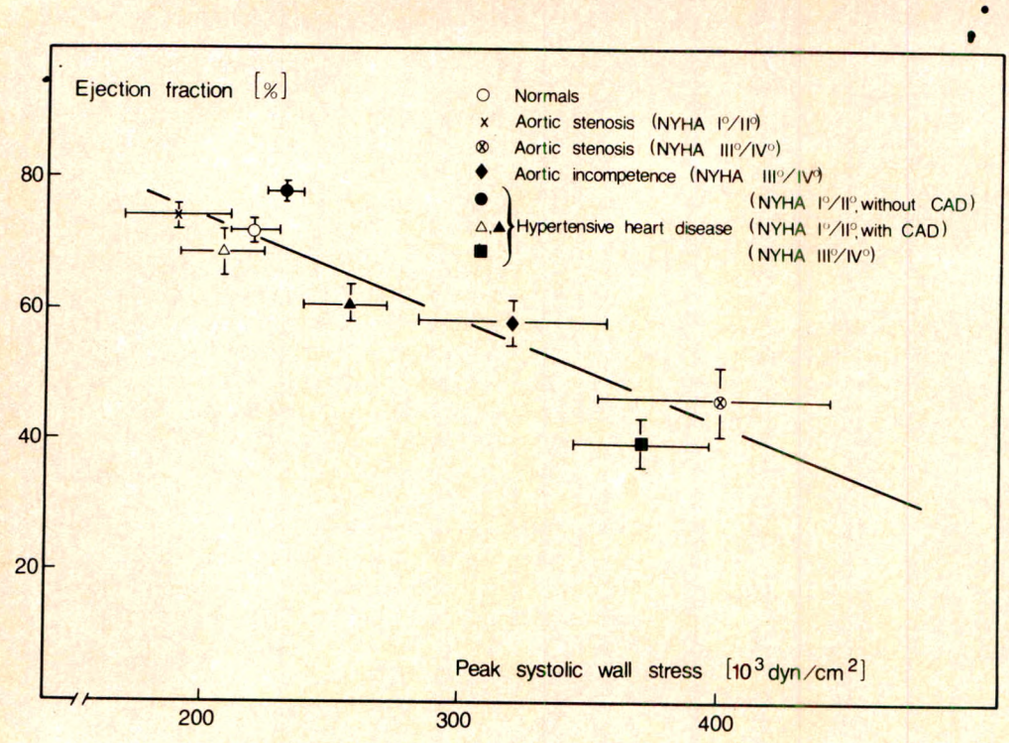

FIGURE 3. Relation between peak systolic wall stress (= left ventricular afterload) and ejection fraction. Note the decrease in ejection fraction with an increase in stress. Abbreviations as in Figure 1.

wall stress at equal mass to volume ratio or to lower mass to volume ratio at equal peak systolic wall stress.

With a chronic pressure load an increase in the mass to volume ratio would be expected. However, correlation between these two variables, that is, between systolic pressure and the mass to volume ratio, was not present (Fig. 2). When all patients are considered with regard to equal peak systolic wall stress (isostress ranges) a graduated arrangement of all values becomes possible (Fig. 2): At comparable systolic pressure the peak systolic wall stress decreases with an increase in the mass to volume ratio. Conversely, at comparable mass to volume ratio the peak systolic wall stress increases with an increase in systolic pressure. However, within any isostress range the peak systolic wall stress remained unaltered even at extreme pressure load, provided the mass to volume ratio increased in proportion to systolic pressure load.

Stress and function: With an increase in peak systolic wall stress a decrease in cardiac function occurred (Table I, Fig. 3). Patients with the largest peak systolic wall stress (decompensated essential hypertension, aortic stenosis and aortic incompetence) had the lowest ejection fraction and lowest ejection phase indexes.

Determinants of myocardial oxygen consumption: Myocardial oxygen consumption per left ventricular weight unit ($M\dot{V}O_2$) was lowest in the normo-

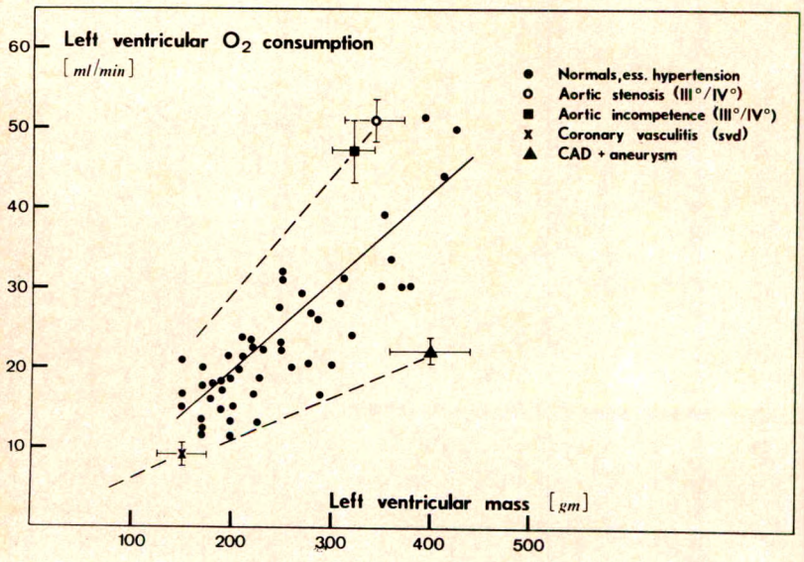

FIGURE 4. Relation between left ventricular mass and left ventricular oxygen consumption. ess. = essential; svd = coronary vasculitis (small vessel disease); other abbreviations as in Figures 1 and 2.

tensive patients with small vessel disease and was largest in those with aortic valve disease with a dilatated heart (Table I). There was no correlation between $M\dot{V}O_2$ and ventricular function (as manifested by cardiac index, stroke work index, external cardiac work, pressure-time index, isovolumic contractility indexes, ejection phase indexes, systolic pressure and other measures).

Total left ventricular oxygen consumption was linearly correlated with total left ventricular muscle mass in normal subjects and in hypertensive patients with normal stress hypertrophy (Fig. 4). At comparable left ventricular mass increased oxygen consumption occurred in patients with high stress hypertrophy due to decompensated aortic stenosis and aortic incompetence (functional classes III and IV), whereas decreased oxygen consumption was found in those with coronary artery disease, aneurysm or small vessel disease.

The mass to volume ratio was inversely related to $M\dot{V}O_2$ (Table I, Fig. 5). At isobaric conditions, the largest mass to volume ratio and lowest $M\dot{V}O_2$ was found in patients with hypertrophic obstructive cardiomyopathy, whereas in those with decompensated aortic stenosis and aortic incompetence the lowest mass to volume ratio was associated with the largest $M\dot{V}O_2$. Normotensive patients with normal left ventricular function or with coronary artery disease had a lower $M\dot{V}O_2$ at a comparable mass to volume ratio.

Because the mass to volume ratio, at equal systolic pressure, represents the major determinant of peak systolic wall stress, correlation was performed between peak systolic wall stress and the $M\dot{V}O_2$. A significant relation was found between both variables (Fig. 6). Patients with decompensated aortic stenosis and aortic incompetence were within the upper range, and the normotensive normal subjects were within the lower range of this relation. Extrapolation to zero stress resulted in an intercept of 3.28 ml/min × 100 g (Fig. 6). This value, although somewhat increased, corresponds quite well with the oxygen consumption of the empty

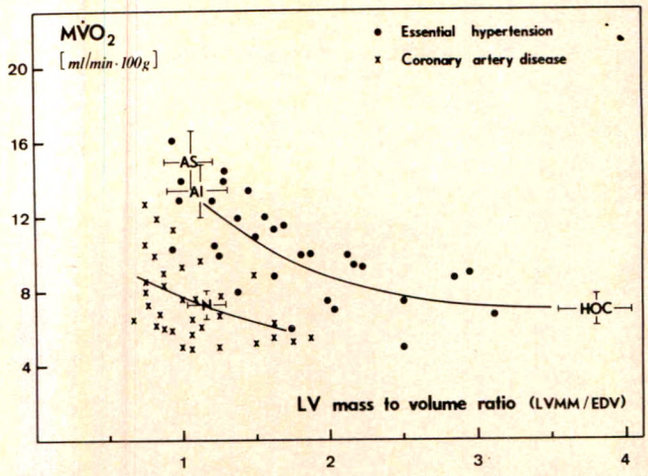

FIGURE 5. Relation between left ventricular (LV) mass to volume ratio (LVMM/EDV) and left ventricular oxygen consumption per weight unit ($M\dot{V}O_2$). AI = aortic incompetence; other abbreviations as in Figures 1 and 2.

beating heart.[18] Steepness of this regression indicates an increase in $M\dot{V}O_2$ by 2.8 ml/min × 100 g for an increase in peak systolic wall stress by 100 (10^3 dynes/cm^2) for normal subjects as well as for those with coronary artery disease and hypertrophic heart disease.[19]

Systolic stress reserve: The lowest peak systolic wall stress, which was found in patients with chronic hypertensive hypertrophy, was 100 ± 12 (10^3 dynes/cm^2) and the largest peak systolic wall stress was 450 ± 46 (Table III). In comparison with the normal subjects (peak systolic wall stress = 220 ± 9 × 10^3 dynes/cm^2), patients with chronic hypertrophy may have a decreased, normal or increased peak systolic wall stress. Thus, both low and high stress hypertrophy may occur, the ratio between maximal and minimal stress averaging 4.5 (Table III).

Coronary reserve: This was determined in 12 normal subjects and averaged 4.9. In patients with essential

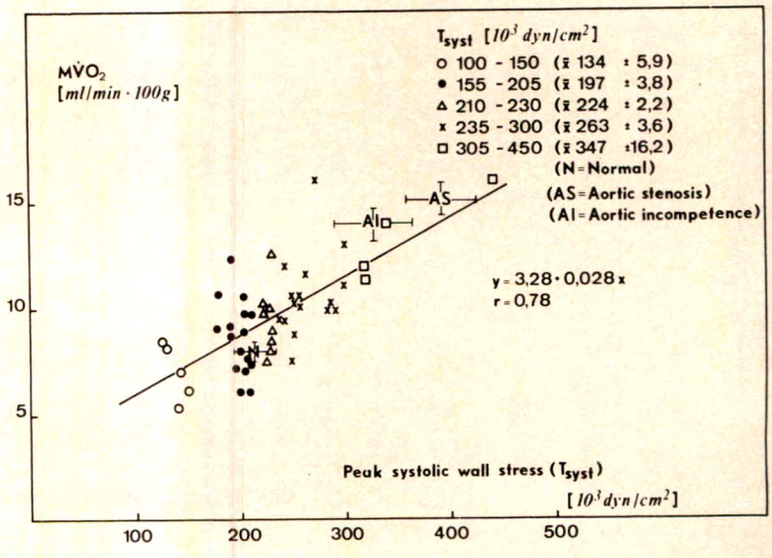

FIGURE 6. Relation between peak systolic wall stress and left ventricular oxygen consumption per weight unit ($M\dot{V}O_2$). Note the significant relation between both variables. Unidentified abbreviations as in Figure 1.

TABLE III

Minimal and Maximal Values of Peak Systolic Wall Stress

	Minimum	Maximum	$\frac{\text{Maximum}^{\S}}{\text{Minimum}}$
T_{syst} (10^3 dynes/cm^2)*	100 ± 12	450 ± 46	4.5 = stress reserve
$\dot{M}VO_2$ (ml/min × 100 g)†	5.2 ± 0.3	24 ± 2.9	4.6 = metabolic reserve
$\dot{V}_{cor}$ (ml/min × 100 g)‡	79 ± 12	392 ± 26	4.9 = coronary reserve

All values (maximal versus minimal) $P < 0.001$.
* Essential hypertension.
† Chronic valvular and hypertensive pressure overload.
‡ Normal subjects (before and after administration of dipyridamole, 0.5 mg/kg).
§ The ratio (maximum/minimum) has been defined as stress reserve, metabolic reserve and coronary reserve, respectively.
$\dot{M}VO_2$ = myocardial oxygen consumption; T_{syst} = peak circumferential systolic wall stress; $\dot{V}_{cor}$ = coronary blood flow.

hypertension, a decrease in coronary reserve was found with an increase in peak systolic wall stress and a decrease in the mass to volume ratio (Fig. 7).

Discussion

Systolic wall stress is the consequence of changes in mass, ventricular volume and systolic pressure. In *acute* pressure overload, systolic stress increases in parallel with an increase in pressure because the mass to volume ratio (or wall thickness to radius ratio) remains nearly unaltered. In *chronic* pressure and volume overload, systolic stress is altered in accordance with chronically altered left ventricular geometry (mass to volume ratio). In either condition, systolic stress reflects the response in ventricular hypertrophy to the acute or chronic left ventricular overload. Therefore, left ventricular hypertrophy may be appropriate or inappropriate with regard to the systolic stress changes that depend on the mass or volume changes relative to load.[20–22] This concept implies that systolic stress represents the afterload imposed on the left ventricular wall.[2,20,22]

Appropriateness of left ventricular hypertrophy: This study has shown that the degree or appropriateness of left ventricular hypertrophy may be described by: (1) the relation between the mass to volume ratio

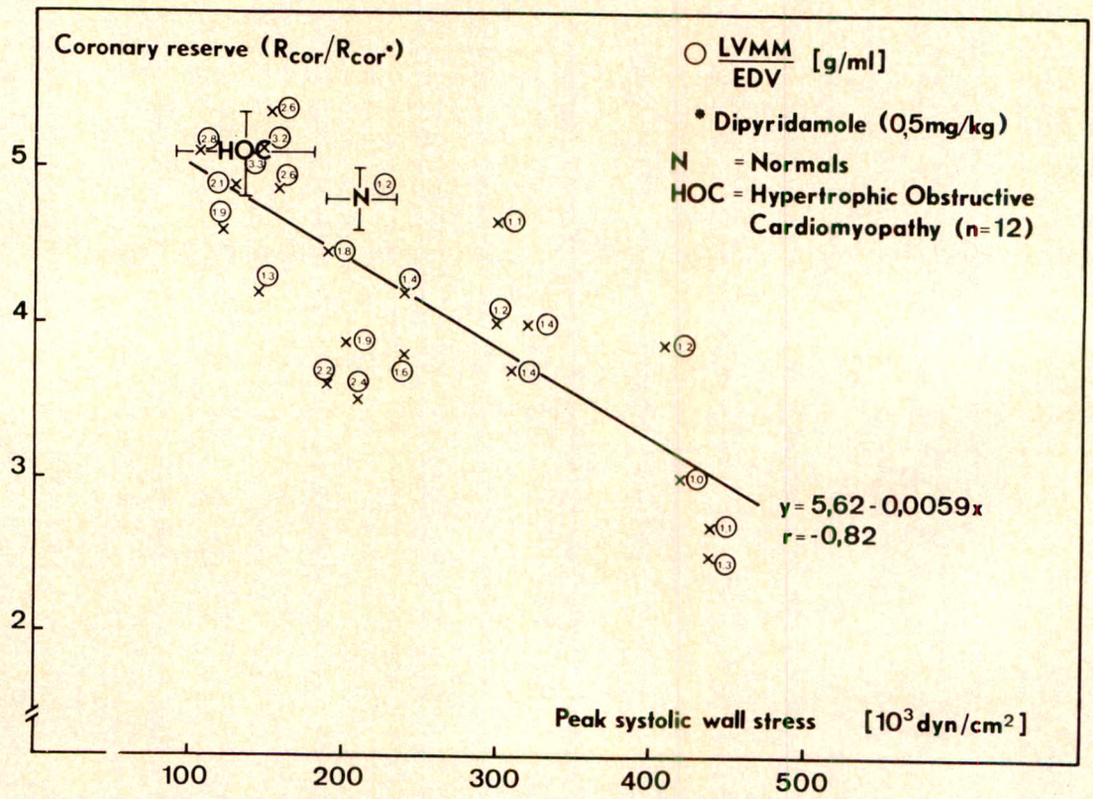

FIGURE 7. Relation between peak systolic wall stress and coronary reserve in the normal subjects and in patients with hypertrophic obstructive cardiomyopathy (HOC) and essential hypertension (**crosses**). **Encircled numbers** represent the mass to volume ratio (LVMM/EDV); other abbreviations as in Figure 1.

and peak circumferential systolic wall stress (Fig. 1), or (2) the relation among systolic pressure, mass to volume ratio and peak systolic wall stress when considering instantaneous systolic pressure (Fig. 2). With regard to this relation at least three types of left ventricular hypertrophy may be separated in chronic hypertrophic heart disease[20,22,23] (Fig. 6): (1) *appropriate hypertrophy,* which keeps peak systolic stress normal even at an extreme pressure load, as a result of an appropriate increase in mass to volume ratio parallel with pressure load; (2) *inappropriate excess hypertrophy (low stress hypertrophy),* which is associated with a marked increase in left ventricular mass out of proportion to intraventricular volume; and (3) *inappropriate low hypertrophy (high stress hypertrophy),* which is characterized by excess ventricular dilatation out of proportion to ventricular mass development. Thus, at least two forms of inappropriate hypertrophy may occur in chronic hypertrophic heart disease.

Appropriateness of left ventricular hypertrophy, ventricular function and $M\dot{V}O_2$: The degree of appropriateness of left ventricular hypertrophy profoundly influenced both left ventricular function and myocardial oxygen consumption (Fig. 8): (1) Hypertrophy with an increase in wall stress associated with normal or decreased mass to volume ratio; this was regularly associated with increased $M\dot{V}O_2$. Ventricular performance was depressed under these conditions, and left ventricular hypertrophy was inappropriate and out of proportion to the pressure and volume demand of the left ventricle. (2) Hypertrophy associated with normal wall stress and normal left ventricular function and $M\dot{V}O_2$; left ventricular hypertrophy was appropriate with regard to the pressure and volume demand. (3) Hypertrophy associated with low peak systolic wall stress and large mass to volume ratio; there was normal or increased left ventricular function and normal or decreased $M\dot{V}O_2$. Left ventricular hypertrophy was inappropriate, that is, out of proportion to the pressure and volume demand of the left ventricle.

The existence of both low and high stress hypertrophy in chronic heart disease may help to explain the difference in oxygen demand as well as the variable results that have been reported for left ventricular oxygen consumption in patients with a chronically hypertrophied heart. For example, in aortic stenosis a 4.14-fold variation in $M\dot{V}O_2$ has been reported (from 5.8 to 24 ml/min × 100 g).[18,20,24] In essential hypertension the range of $M\dot{V}O_2$ extends from approximately 5.2 to 16 ml/min × 100 g (3.1-fold).[19–21] These variations seem controversial and may be due in part to variations in heart rate, cardiac work or contractility. There is little question that contractility or acute inotropic interventions, or both, may modify the $M\dot{V}O_2$, although the role of contractility in influencing the overall oxygen consumption in the chronically diseased hypertrophic and failing human heart has not yet been clearly identified.[25–27] It appears somewhat surprising that a large $M\dot{V}O_2$ was found in patients with the lowest values for left ventricular function and contractility and the lowest $M\dot{V}O_2$ was present in patients with normal left ventricular function and contractility, particularly in those with essential hypertension, who had significant increases in the maximal rate of pressure development

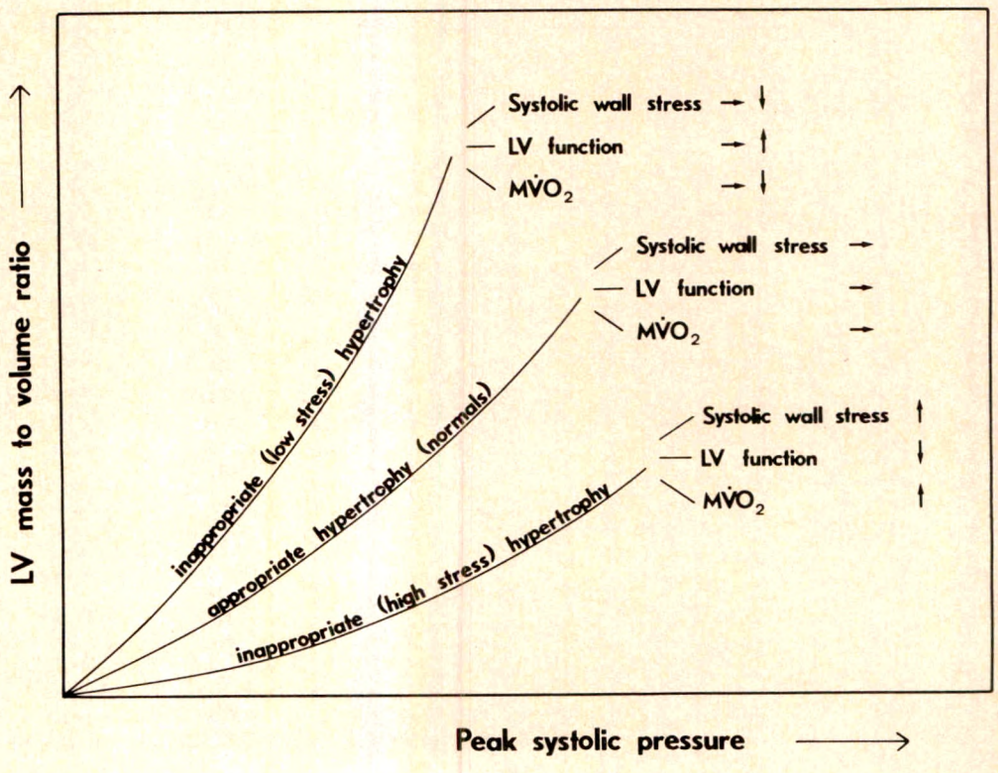

FIGURE 8. Classification of hypertrophic heart disease with regard to the degree or appropriateness of left ventricular (LV) hypertrophy (see Figure 2). $M\dot{V}O_2$ = myocardial oxygen consumption.

(dP/dt_{max}) (Tables I and II). This result may be the consequence of a minor influence of contractility on overall $M\dot{V}O_2$ in chronic heart disease, or the result of a disproportionate interplay between the contractile state and systolic wall stress in favor of a dominant influence of peak systolic wall stress on cardiac oxygen demand. In a quantitative sense, systolic wall stress, as demonstrated by our study, may play the major role and may predominantly influence $M\dot{V}O_2$. Thus, a depressed contractile state may be associated with an increase in $M\dot{V}O_2$ when peak systolic wall stress is increased (essential hypertension group IV, aortic stenosis and aortic incompetence in functional classes III and IV), and decreased $M\dot{V}O_2$ may be present during normal contractility when peak systolic wall stress is decreased (essential hypertension group I, aortic stenosis and aortic incompetence in functional classes I and II).

Pressure-induced stress alterations and $M\dot{V}O_2$: An increase (hypertensive crisis) or decrease (antihypertensive treatment) in systolic pressure is associated with alterations in systolic wall stress and, hence, in $M\dot{V}O_2$. However, pressure-induced stress alterations depend on the individual isobaric conditions as well as on the initial mass to volume ratio (Fig. 9). An equal rise in pressure (for example, from 120 to 200 mm Hg) (A′ → B′, Fig. 9) at a mass to volume ratio of 4 g/ml leads to a stress increase of only 80×10^3 dynes/cm^2, whereas the same rise in pressure (A → B) at a mass to volume ratio of 1.2 is followed by a considerable increase in stress of 180×10^3 dynes/cm^2. The same calculations and consequences as to systolic stress and, hence, $M\dot{V}O_2$ are valid for therapeutically induced pressure reductions. This means that from a diagnostic and prognostic point of view, a rise in systolic pressure in a dilated hypertensive heart causes a greater increase in peak systolic wall stress and in $M\dot{V}O_2$ than the same pressure increase in a nondilated, hypertensive heart. Because both stress and metabolic reserve are limited in man, the left ventricular stress capacity is increasingly reduced with: (1) an increase in initial systolic stress, (2) a decrease in mass to volume ratio, and (3) an increase in systolic pressure.[20] However, a therapeutic reduction in systolic pressure will lead to greater reduction in both stress and oxygen consumption in patients with left ventricular dilatation than in patients with concentric hypertrophy (Fig. 9). Thus, the relation between mass to volume ratio and peak systolic wall stress elucidates the importance of pressure-dependent changes in systolic stress and, hence, in myocardial stress and metabolic reserve.

Coronary reserve, systolic wall stress and $M\dot{V}O_2$: The decrease in coronary reserve with the increase in peak systolic wall stress may be referred to the increase in $M\dot{V}O_2$ in parallel with augmentation of peak systolic wall stress (Fig. 7). Because a rise in $M\dot{V}O_2$ is accomplished by a rise in coronary flow, the latter is already increased at resting conditions. Consequently, the dipyridamole-estimated coronary reserve becomes progressively decreased with an increase in $M\dot{V}O_2$, with a decrease in the mass to volume ratio and with an increase in systolic wall stress. The coronary reserve would be influenced by myocardial contraction abnormalities as well as by coronary arterial lesions, primarily as a result of coronary stenosis[17,24]: (1) In patients with coronary artery disease a marked decrease in coronary reserve (mean 2.01 ± 0.12) was found.[17] This is most obviously due to coronary atherosclerosis and, hence,

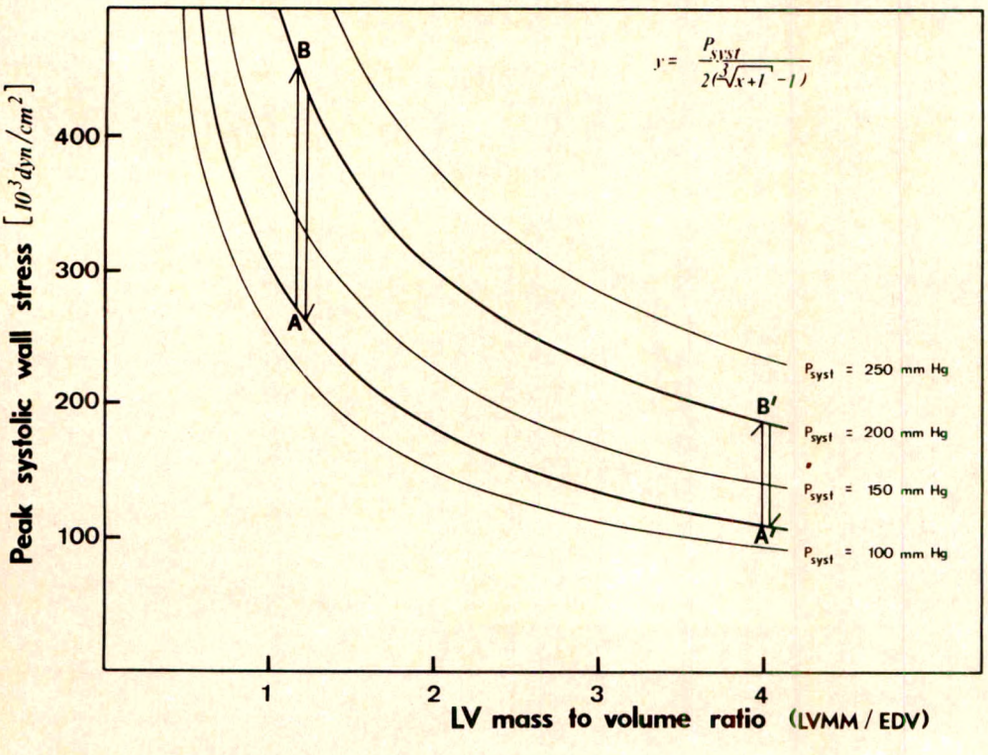

FIGURE 9. Relation between left ventricular (LV) mass to volume ratio (LVMM/EDV) (x) and peak systolic wall stress (y) at different isobaric conditions. P_{syst} = peak systolic pressure.

to the impaired dilating capacity of the coronary vascular bed. (2) In vasculitis, lupus erythematosus and in scleroderma heart disease a considerable reduction in coronary reserve may occur even with normal coronary arteries and normal heart size. This has been referred to as vasculitic involvement of the small coronary arteries, which in a great percentage of cases are histologically affected.[15,17] (3) Independent from coronary lesions the coronary reserve may even be greatly reduced in left ventricular enlargement associated with high end-diastolic pressure. In these diseases (congestive heart failure, congestive cardiomyopathy, for example) an increased myocardial, that is, extravascular, component will be responsible for the decrease in coronary reserve.[28] This may be attributed to enhancement of the extracoronary tissue resistance, reduction in the driving coronary perfusion pressure and impaired course of contraction and relaxation and, hence, to impaired coronary perfusion. (4) Finally, clinical diseases with an increased resting $M\dot{V}O_2$ (high stress hypertrophy, for example, in decompensated hypertrophic heart disease) may limit coronary reserve. Thus, the coronary reserve depends on coronary and extracoronary (that is, myocardial) factors. In a quantitative sense, the coronary lesions may affect or reduce the coronary reserve more than extravascular and myocardial abnormalities.[17]

Relations among coronary, metabolic and systolic stress reserves: A close relation seems to be present among the coronary,[5,10] metabolic[5,7] and systolic stress reserves[5,6] of the left ventricle (Table III). This obviously helps to explain the limited left ventricular function or reserve capacity or both, in disorders associated with coronary (for example, in coronary artery disease), metabolic (for example, in hyperthyroidism) and systolic wall stress abnormalities (for example, in decompensated left ventricular pressure overload). Because the human heart works almost exclusively aerobically, an increase in left ventricular function may be accomplished preferably by an increase in myocardial oxygen supply. In coronary artery disease, the coronary reserve is limited because of coronary stenosis. Accordingly, the coronary factor is the limiting link that diminishes the oxygen availability to the myocardium, thereby restricting both the metabolic and systolic stress reserves. In hyperthyroid heart disease an increased $M\dot{V}O_2$ occurs due to excess increase in heart rate, cardiac output and contractility,[29,30] thus narrowing both the coronary and systolic stress reserves. Here, the increased metabolism seems to play the limiting role. In decompensated left ventricular pressure overload, as has been shown previously, both the coronary and metabolic reserves are reduced because the stress level is already elevated at rest. Thus, increased left ventricular loading conditions at rest may skim off maximal stress capacity.

It is concluded from these results that systolic wall stress reflects the major determinant of the degree of left ventricular hypertrophy and plays a predominant role in both left ventricular function and myocardial energy balance. The coronary, metabolic and systolic stress reserves of the human heart seem to be closely correlated with each other, and it is reasonable to assume that determination of coronary reserve gives important insight into the left ventricular metabolic and working capacity reserves.

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Temporal Relation Between Onset of Cell Anoxia and Ischemic Contractile Failure

Myocardial Ischemia and Left Ventricular Failure in the Isolated, Perfused Rabbit Heart

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Contractile dysfunction is characteristic of the acutely ischemic myocardium. This study was undertaken to assess the temporal relations between the onset of cell anoxia and ischemic contractile failure in isolated, isovolumetric contracting rabbit hearts. High speed epicardial fluorescence photography using reduced nicotinamide adenosine nucleotide (NADH) was used to identify areas of cell anoxia. The onset of ischemia was correlated with deterioration of pressure generation over the course of sequential 60 second coronary arterial occlusions. In the isovolumetric contracting rabbit heart, areas of ischemia were detected 2 seconds after coronary occlusion. Significant reduction in peak systolic pressure occurred at 6 seconds of ischemic time and pressure continued to decrease throughout the 60 second period of coronary occlusion. NADH accumulation indicates imbalance of myocardial oxygen supply and demand and the cessation of oxygen utilization by the mitochondria. The results of this study indicate that ischemia is detectable within 1 to 2 seconds after coronary occlusion and that ischemic ventricular dysfunction occurs several seconds thereafter. Myocardial oxygen reserve is negligible.

In the absence of angina pectoris or antecedent myocardial infarction, patients with coronary artery disease do not typically exhibit left ventricular dysfunction. Transient ischemia has been correlated with transient left ventricular failure by Herman et al.[1] In experimental coronary arterial occlusion the central ischemic zone contracts poorly. However, Katz[2] demonstrated a compensatory increase in contractility of adjacent nonischemic myocardium. In an attempt to establish the relation between myocardial oxygen supply, energy production and ventricular contractility, Covell et al.[3] studied open chest dogs during coronary arterial ligation. A biopsy of the poorly contractile ischemic myocardium was performed and persistently normal levels of high energy adenosine triphosphate (ATP), and creatinine phosphate were found long after ventricular dysfunction had developed. The heart does not simply lose energy during early ischemia. The mechanism by which inadequate oxygen supply leads to reduced myocardial contractility is not clear. A better understanding of this sequence should precede any rational approach to therapy. As a basis for unraveling this relation, the temporal association between tissue hypoxia and reduced ventricular function must be established.

Barlow and co-workers[4,5] devised a technique for assessing myocardial oxygen supply and demand based on the fluorescent characteristics of nicotinamide adenine dinucleotide (NAD), a component of the in-

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tramitochondrial electron transport system. With insufficient oxygen supply, NAD is reduced to NADH. NADH fluoresces when excited by ultraviolet light; NAD does not.

The purpose of this study was to determine the temporal relation between myocardial hypoxia, mitochondrial pyridine nucleotide reduction and ventricular contractile performance utilizing high speed epicardial NADH fluorescence photography.

Methods

Experimental procedure: Eight New Zealand male rabbits weighing 2 kg were anesthetized with 50 to 75 mg/kg body weight of sodium pentobarbital intravenously. The heart was rapidly excised and placed on a modified Langendorff apparatus. Perfusion was maintained with Krebs-Ringers bicarbonate buffer solution containing 5 millimolar (mM) glucose and 2.5 mM calcium saturated with 95 percent oxygen and 5 percent carbon dioxide. The perfusate was warmed to 37° C in a heat exchanger and the perfusion pressure was maintained at 75 mm Hg.

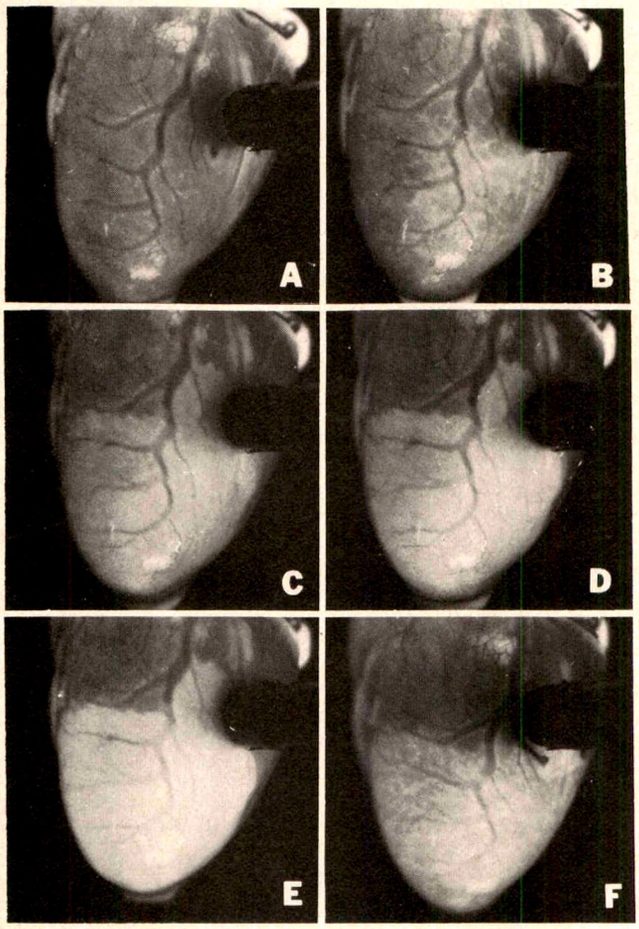

FIGURE 1. Epicardial NADH fluorescence photograph of an isolated rabbit heart. The noose occluder is seen at **upper right.** Two small areas of epicardial fat can be seen to fluoresce on the surface of the left ventricle (**pale areas**). **A,** control photograph taken 1 second before coronary occlusion. **B,** after 5 seconds of ischemia, islands of cell anoxia appear distal to the occluder. **C,** after 10 seconds of ischemia, the anoxic islands coalesce to form an area of nearly homogeneous fluorescence. **D,** 15 seconds of ischemia; **E,** 60 seconds of ischemia. The ischemic portion of the left ventricle reveals a homogeneous distribution and intensity of NADH fluorescence. **F,** 5 seconds of reflow. Areas of diminished NADH fluorescence are apparent, indicating cell reoxidation and resumption of oxygen utilization.

A coronary artery on the anterior surface of the left ventricle was identified and encircled with a ligature. The suture was drawn through a 1.5 mm metal tube to provide a mechanism for standard and reversible noose occlusion.

A small latex balloon was inserted through the mitral valve into the left ventricle and secured with a purse-string suture placed around the mitral anulus. This provided for isovolumetric ventricular contraction. The balloon pressure was monitored with a Statham P23Db pressure transducer and recorded on an Electronics for Medicine DR12 recorder equipped with a differentiating circuit. This allowed continuous measurement of the time derivative of left ventricular pressure. Graham et al.[6] have shown that by inflating the balloon with saline solution to an end-diastolic pressure of 0 a reproducible working heart model is produced. With the balloon deflated, the isolated heart did no external pressure or flow work.

Measurements: Myocardial oxygen consumption ($M\dot{V}O_2$) was measured during both working and nonworking conditions. A stiff multiholed plastic cannula was secured in the pulmonary artery and connected to an oxygen electrode of the Clark type to continuously record the oxygen tension (PO_2) of the coronary venous effluent. Coronary flow was measured by the time collection of effluent from the Clark electrode and thebesian flow that dripped from the heart. After each experiment the heart was blotted and weighed. All hearts were paced at a rate of 240 beats/min utilizing bipolar atrial electrodes and a Grass SD9 stimulator.

Myocardial oxygen consumption ($M\dot{V}O_2$) was calculated according to the formula: $M\dot{V}O_2$ = (partial pressure of arterial oxygen minus partial pressure of venous oxygen) × 0.00003 ml O_2/torr × coronary flow/g wet weight of the heart where 0.00003 ml O_2/torr is the solubility coefficient of oxygen dissolved in each ml of perfusate at 37° C. $M\dot{V}O_2$ is expressed as microliters of oxygen consumed per minute per gram wet weight of heart.

NADH fluorescence photographic technique: We utilized a modification of the technique originally described by Barlow and Chance.[4] Epicardial NADH fluorescence photographs were taken with either a Palliard-Bolex® 16 mm movie camera or a Nikon® 35 mm SLR camera equipped with an autowinder. A Wratten 2E filter was placed over the camera lens to allow transmission of emitted NADH fluorescence in the 430 to 510 nm region. Fluorescence excitation was provided by two water-cooled xenon flash tubes (400 joules each, E.G. and G. Corp. FX-47C3) mounted on both sides of the camera lens. Each flash tube was covered with a Corning 5840 filter to provide incident light of 330 to 380 nm. The flash tubes and cameras were all synchronized with the pacing stimulus. Movie camera speed was 4 frames/sec (1 frame/heartbeat) or 1 frame/sec (1 frame/4 heartbeats) with the Nikon camera.

Control NADH fluorescence photographs were taken and oxygen consumption was recorded. The coronary artery was then occluded for 60 seconds and fluorescence photographs were taken during this time. Still photographs were taken 1 second before occlusion at each of the first 15 second periods after occlusion, and at 30, 45 and 60 seconds thereafter. The occlusion was then released. A photograph was taken at each of the first 10 seconds of reperfusion. The movie camera allowed a continuous record of the entire cycle up to 60 seconds of reperfusion.

After a 5 minute recovery period, after the balloon was inflated. Stable working heart conditions were monitored for an additional 5 minutes. A control photograph was taken and

oxygen consumption recorded and the 60 second cycle of ischemia was repeated. Intraventricular pressure and its derivative (dP/dt) were recorded before and throughout this cycle of ischemia.

All values are expressed as mean ± standard error of the mean. Differences were assessed using a t test for paired data.

Results

Control: Control epicardial NADH fluorescence photographs under both working and nonworking conditions demonstrated minimal fluorescence and appeared uniformly dark (Fig. 1A and 2A). The atria and epicardial fat fluoresce because of the presence of fluorochromes in these tissues. Oxygen consumption in nonworking and working heart preparations was 86.14 ± 7.04 μl and 99.19 ± 8.01 μl O_2/min per gram wet weight, respectively ($P = 0.025$). Peak systolic intraventricular pressure was 48.1 ± 4.0 mm Hg in preparations with an end-diastolic pressure of 0. Peak first derivative of left ventricular pressure (dP/dt) was 1058.9 ± 71.2 mm Hg/sec.

Ischemia: In nonpressure-generating, nonworking hearts, increased epicardial NADH fluorescence was detectable within 2.7 ± 0.4 seconds after coronary occlusion (range 2 to 4 seconds). The segment was completely fluorescent within 11.2 ± 0.3 seconds (Fig. 1). There was a slight increase in the intensity of fluorescence at the end of 60 seconds but the distribution was unchanged. After release of occlusion, areas of decreased fluorescence indicating resumption of oxygen utilization were always detectable within 1 second of reperfusion. The intensity of fluorescence returned to control levels within 10 to 20 seconds after restoration of flow.

When the cycle of ischemia was repeated during pressure-generating working conditions the onset of a detectable increase in fluorescence occurred earlier (1.7 ± 0.3 seconds, range 1 to 2 seconds) ($P < 0.05$) than during nonworking conditions (Fig. 2). Although maximal fluorescence occurred earlier (9.3 ± 0.8 seconds) during working conditions, this difference was not significant ($P < 0.10$).

The distribution of fluorescence in working and nonworking preparations was not different and the time course of recovery was also unchanged. Reversing the sequence of nonworking and working observations did not alter the corresponding appearance of fluorescence. During the course of the experiment work was always associated with the earlier onset of ischemia regardless of when the latter occurred.

Peak systolic intraventricular pressure decreased within the first 2 seconds after the onset of coronary occlusion (Fig. 3). This decrease became significant at 6 seconds of ischemic time ($P < 0.05$). Pulsus alternans was frequently seen during the first 10 to 15 seconds after coronary occlusion. Peak systolic pressure continued to deteriorate throughout the ensuing period of ischemia and at the end of 60 seconds was 62.9 percent of the control value ($P < 0.01$). Peak dP/dt decreased similarly and was different from the control value at 7 seconds (Fig. 4). The time course for recovery of contractile performance was not examined by these studies.

Discussion

Chance et al.[7] and Jobsis[8] reported that the reaction of oxygen with cytochrome a_3 at the terminal end of the electron transport system accounts for more than 90 percent of the oxygen consumed by mammalian tissues. The electron transport chain is a series of oxidation-reduction couples permitting the orderly, stepwise degradation and transfer of the free energy difference

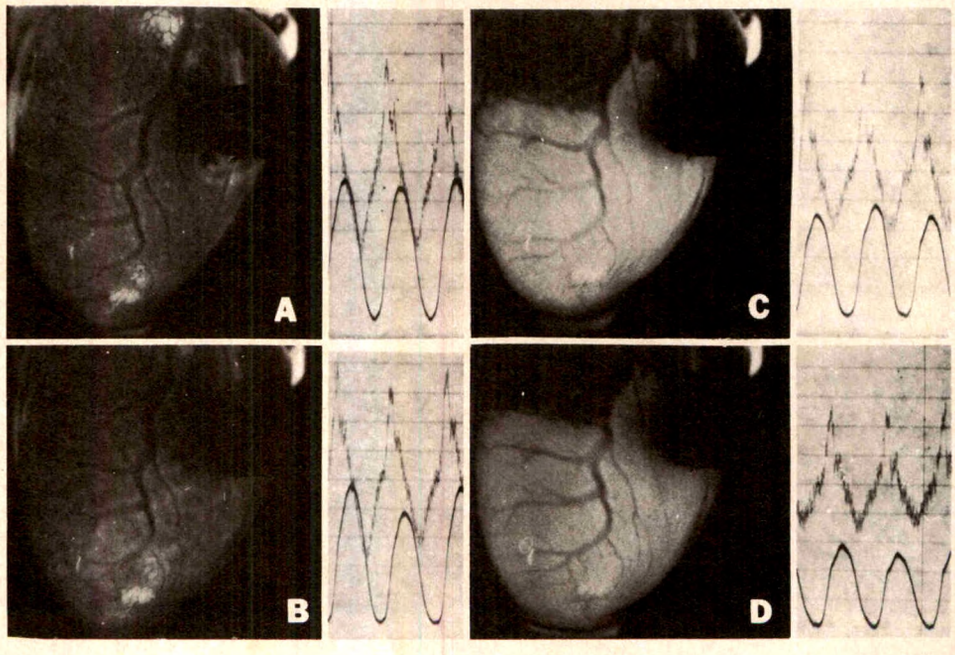

FIGURE 2. Epicardial NADH fluorescence photograph of the working, isolated rabbit heart seen in Figure 1. Pressure recordings appear at right. The **top tracing** on each recording shows the first derivation of left ventricular pressure (dP/dt). **The bottom tracing** shows intraventricular pressure. **A,** control photograph and pressure recordings. End-diastolic pressure is 0. Peak systolic pressure is 45 to 47 mm Hg. **B,** 5 seconds of ischemia. Islands of anoxia are present distal to the occluder. Mean ventricular pressure has decreased slightly. Pulsus alternans, an early sign of ischemic ventricular dysfunction, may be seen in this tracing. **C,** 15 seconds of ischemia. Distribution of ischemia is complete. A significant decrease in peak systolic pressure and contractility is apparent. **D,** 60 seconds of ischemia. Distribution of ischemia is unchanged from the distribution of ischemia during nonworking conditions in the same heart (Fig. 1E). A marked decrease in systolic pressure and contractility has occurred.

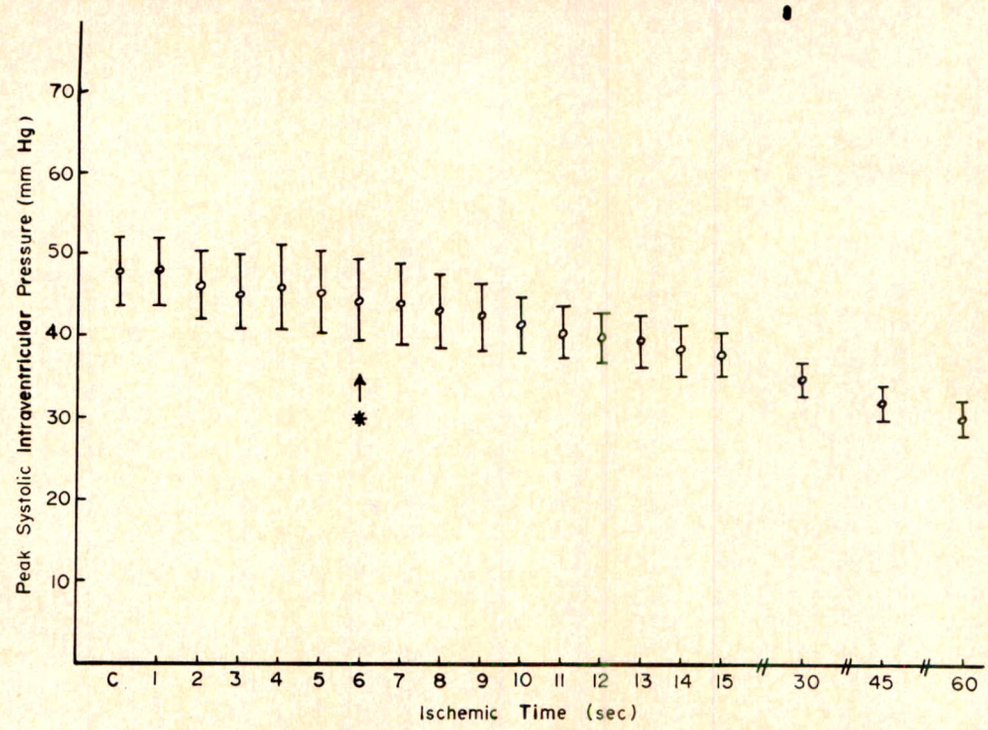

FIGURE 3. Peak systolic intraventricular pressure (mean ± standard error of the mean). The decrease in peak pressure development occurs within 2 to 3 seconds after coronary occlusion. At 6 seconds (**asterisk**) of ischemia, the level of peak systolic pressure differs from the control value ($P < 0.05$).

between NADH (or reduced flavoproteins) and oxygen. This free energy is converted into high energy phosphate bonds in a process termed oxidative phosphorylation. Chance[9] demonstrated that the oxygen concentration at the mitochondrial level sufficient to permit this process is on the order of 10^{-7} M or 0.07 torr.

Myocardial oxygen tension, cell anoxia and contractile dysfunction: Tennant and Wiggers[10] recognized the early onset of contractile abnormalities of the ischemic myocardium. More recently, Sayen et al.,[11] utilizing intramyocardial polarographic oxygen electrodes in the beating canine heart, demonstrated the rapid decrease in myocardial oxygen tension and onset of contractile dysfunction after coronary arterial occlusion. In their studies the decrease in polarographic oxygen was 50 percent complete at the end of 4 to 21 seconds and 90 percent complete at the end of the first 50 seconds. The onset of contractile failure often preceded the decrease in polarographic oxygen. Our study identifies an even closer association between these events.

Ischemia resulted in the appearance of anoxic cells (areas of increased epicardial fluorescence) within 1 to 2 seconds after coronary occlusion in the isolated crystalloid-perfused working rabbit heart. The onset of contractile dysfunction occurred at the same time (Fig. 3 and 4). This decline in ventricular performance became statistically significant at 6 seconds of ischemic time. Subsequently, although cell anoxia in the ischemic segment was complete within 15 seconds, contractile performance continued to deteriorate up to the time when flow was restored at 60 seconds.

Mechanism of contractile dysfunction of ischemic myocardium: Katz[2] and Hillis and Braunwald[12] have discussed the possible mechanisms responsible for contractile dysfunction of the ischemic myocardium. Because the principal function of the mitochondria is the production of adenosine triphosphate (ATP), loss of mitochondrial ATP production during ischemia might well represent the mechanism underlying contractile dysfunction. As available oxygen is depleted, electron flux stops and ATP production abruptly halts. Available cytosolic creatine phosphate and ATP become depleted. In the absence of substrate and ATP, contraction abruptly stops. Although this explanation is attractive, extensive experimental evidence does not support it.

Braasch et al.[13] and Katz[2] demonstrated that, although phosphocreatine content in the myocardial cell declines sharply shortly after the induction of ischemia, the ATP content of myocardial biopsy sections remains elevated at levels exceeding that necessary to contraction long after tension development has stopped. If total tissue ATP concentration remains normal, perhaps this high energy compound is depleted selectively at certain critical intracell sites. Indeed, Shrago and Sul[14] recently demonstrated inhibition of mitochondrial adenine nucleotide translocase activity, which may result in sequestration of ATP within the mitochondria making

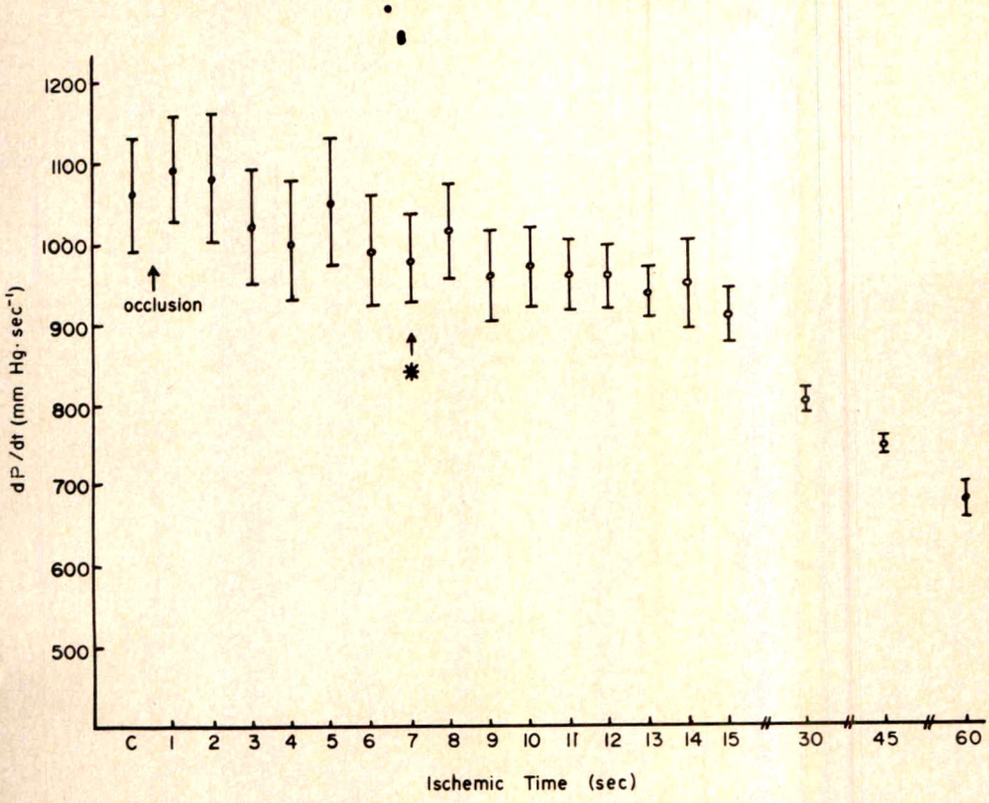

FIGURE 4. Ventricular contractility and first derivative of left ventricular pressure peak (dP/dt) (mean ± standard error of the mean). The decrease in contractility follows a time course similar to that of peak pressure development. At 7 seconds (**asterisk**) of ischemia, the value for contractility differs from the control value ($P < 0.05$).

it unavailable for extramitochondrial utilization. Kubler and Katz[15] pointed out that, if a critical shortage of ATP were the cause of loss of tension development by the ischemic myocardium, the myocardium would display rigor, not loss of tension.

Recent evidence[12,16] implicates intracell acidosis as a likely mediator of contractile failure. Williamson[17] demonstrated that the rate of myocardial lactate accumulation reaches its maximum during the 1st minute of ischemia. Jennings et al.[18] showed that hydrogen ion excess sufficient to reduce intracell methylene blue occurs within 8 to 10 seconds after the induction of ishcemia. That accumulating hydrogen ion interferes with the interaction between calcium and contractile proteins has been postulated by Hillis and Braunwald[12] and Katz and Hecht.[16]

Implications: Our data indicate a close temporal correlation betwen the onset of cell anoxia and the initiation of ventricular contractile dysfunction. However, this study does not resolve the issue of whether intracell acidosis or cessation of ATP production is the final mediator of loss of tension development in ischemic myocardium. This is especially true because the onset of NADH fluorescence may indicate the simultaneous occurrence of both processes. This study also supports the concept of a near 0 myocardial oxygen reserve because evidence of cell anoxia is present within several seconds of coronary occlusion.

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Myocardial Oxygen Supply in Left Ventricular Hypertrophy and Coronary Heart Disease

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Coronary arteriolar dilation adjusts blood flow according to local fluctuating metabolic needs of the myocardium. Because of high extravascular compression during systole, the subendocardial layer of the left ventricle is especially dependent on the duration and the perfusion pressure of the diastolic period. In patients with obstructive coronary artery disease, regional arteriolar dilation is utilized to compensate for focal arterial stenoses. Coronary blood flow may be compensated with the patient at rest, but loss of reserve arteriolar dilation limits further adjustment to superimposed transient increases in metabolic needs. Subendocardial perfusion in the region supplied by the stenosed artery is especially vulnerable to shortened diastolic time during tachycardia. In patients with chronic aortic valve disease, the metabolic rate of the left ventricle is increased in proportion to the increases in myocardial mass and work. Coronary blood flow and metabolic rate per gram of the hypertrophied myocardium are normal when the patient is at rest, at the expense of diminished coronary arteriolar reserve. High tissue pressure relative to the diastolic perfusion pressure probably contributes to the diffuse subendocardial ischemia that occurs in these patients during tachycardia.

The coronary circulation is capable of making vasomotor and blood flow readjustments to meet the wide minute to minute fluctuations in metabolic requirements of the myocardium. We will discuss how these same physiologic vasomotor mechanisms are utilized to compensate for pathologic conditions: obstructive coronary artery disease and cardiac hypertrophy associated with excessive increases in heart work. The compensation is partly successful. However, the coronary response to superimposed fluctuating metabolic requirements is impaired when its physiologic mechanisms are partly expended at rest, leading to manifestations of cardiac dysfunction, which are likely to appear initially in a reversible form during periods of acute stress.

Normal Coronary Function

Coronary arteriolar reserve: Metabolism in the heart muscle is dominated quantitatively by conversion of energy released by substrate oxidation into muscle contraction. The amount of oxygen consumed by the heart in this process is governed by the frequency and intensity of its contractions. Any increase in contraction activity and metabolic rate depends on a simultaneous increase in oxygen uptake from the coronary blood. One approach to meeting varying needs of oxygen uptake would be to maintain blood flow at a high level relative to oxygen consumption so that there would be a reserve of oxygen available in the capillary blood. However, blood flow is kept low in proportion to myocardial oxygen consumption. Even with the body at rest and myocardial oxygen consumption at its most conservative level, two thirds of the oxygen is removed from the blood in transit through the cardiac tissue, resulting in a wide coronary arteriovenous oxygen difference—the widest for any

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organ in the body in the resting state. This arrangement demands the deployment of a system for controlling arteriolar resistance that is very responsive to the immediate myocardial nutritional needs. The control system seems to monitor the concentration of a chemical mediator locally released as a product of myocardial energy metabolism,[1] a tactic that is ideally suited to ensure an appropriate relation between local needs and the supply of oxygen.

The capacity for increasing blood flow by arteriolar dilation is referred to as coronary reserve. The coronary reserve appears capable of satisfying the highest level of coronary blood flow needed (although we have but little information regarding the extreme limits of violent exertion). Coronary blood flow in dogs continues to increase in proportion to heart rate up to 250 beats/min.[2] In normal human beings a linear relation between coronary blood flow and heart rate[3] and a constant coronary arteriovenous oxygen difference[4] have been demonstrated up to heart rates of 170/min.

Energy turnover depends on oxygen being accessible to the respiratory enzyme system contained in the mitochondria scattered about the myocardial contractile fibers. Mitochondrial oxygen supply is determined not only by the minute volume of blood flow relative to oxygen consumption, but also by the diffusion distance between the capillaries and the mitochondria. Control of the number of open capillaries provides a means of regulating oxygen supply to the mitochondria, which is independent of a change in minute volume of blood flow as effected by arteriolar dilation.[5,6] Because most coronary capillaries are believed to be open at all times, this mechanism presumably is relatively unimportant in regulating oxygen supply in the heart in comparison with skeletal muscle, for example.

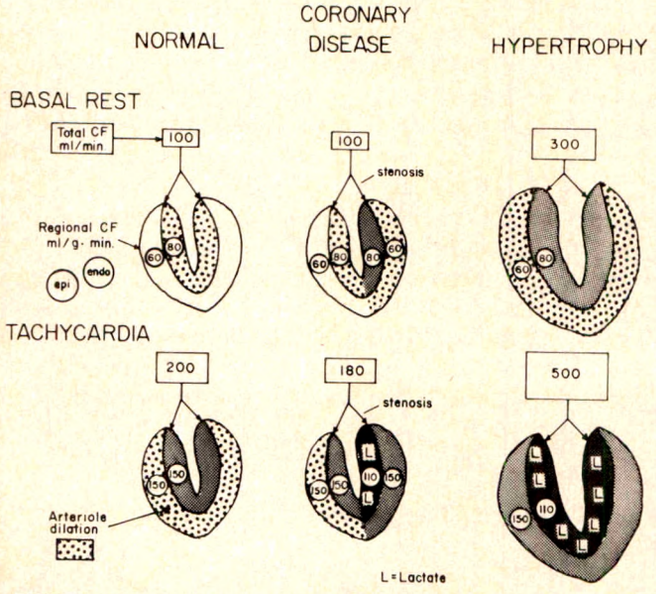

FIGURE 1. Schematic representation of coronary blood flow distribution in the left ventricle at rest and during tachycardia (hypothetical data). **Numbers in rectangles** represent total coronary flow (CF) (ml/min), and **numbers in circles** represent subepicardial (epi) or subendocardial (endo) blood flow (ml/g × min). The intensity of **shading** indicates the intensity of arteriolar dilatation. L represents lactate accumulation due to myocardial hypoxia from ischemia. (1) Normal heart: subendocardial arteriolar dilatation is needed to compete against extravascular compression, especially during tachycardia. (2) Coronary disease with focal coronary stenosis: Extra vasodilation in the region supplied by the stenosed artery maintains normal blood flow distribution at rest. Tachycardia increases the need for blood flow and shortens diastole, impairing subendocardial perfusion. When reserve coronary arteriolar dilatation is exceeded in the subendocardium supplied by the stenosed artery, regional subendocardial hypoxia and lactate production occur. (3) Hypertrophy: a high level of coronary blood flow requires coronary arteriolar dilation at rest. The myocardial hypoxia during tachycardia occurs diffusely throughout the subendocardium.

Transmural blood flow distribution: Resistance to blood flow within the left ventricular muscle is greatly affected by extravascular compression from cardiac contraction, which impedes flow selectively during systole. Compression is greatest in the deep subendocardial layers,[7] yet coronary blood flow is at least as high in the subendocardium as elsewhere,[8] presumably because of lower vascular resistance. When extravascular compression is suddenly removed by cardiac arrest, there is an abrupt marked increase in subendocardial blood flow, as evidence of the underlying lower vascular resistance in that region.[9] Because coronary venous blood oxygen pressure (PO_2) is lower in the subendocardium than in the subepicardium,[10–12] subendocardial perfusion is not increased when compared with local nutritional needs. Maximal arteriolar dilatation induced pharmacologically produces high uniform transmural coronary blood flow.[13,14] Thus, starting from normal basal conditions, coronary reserve appears to be approximately uniform throughout the left ventricle, and the special susceptibility of the subendocardium to ischemia under pathologic conditions cannot simply be attributed to lower initial coronary reserve. We believe its vulnerability is due to its heavy reliance on diastolic perfusion.

Any of the following changes in diastole tend to redistribute blood flow away from the subendocardium: (1) decreased diastolic perfusion pressure[15]; (2) decreased diastolic time due to tachycardia,[8] especially when competing vasomotion is abolished pharmacologically[14] (the vasomotor adjustment normally is only slightly imperfect); and (3) increased diastolic tissue pressure, which compresses intramyocardial blood vessels.[16] The slight transmural shift in blood flow during tachycardia and the compensatory subendocardial arteriolar dilation are represented in Figure 1.

Obstructive Coronary Artery Disease

Coronary vascular compensation at rest: Coronary atherosclerosis narrows the lumens of the large epicardial arteries that conduct blood over the surface of the heart and do not ordinarily offer significant resistance to blood flow. The arterial disease is focal and induces corresponding focal vasomotor adjustments. When an epicardial artery of a conscious dog at rest is moderately narrowed, for example, by graded inflation of an implanted pneumatic cuff, there is no change in blood flow through the artery or in its distribution across the heart wall. The increased resistance offered

by the focal stenosis is matched by a decrease in resistance of the downstream arterioles in that region of the heart (Fig. 1). Presence of the compensatory arteriolar dilation can be disclosed in two ways. First, the intracoronary pressure distal to the stenosing cuff decreases which indicates that an original larger decrease in pressure across the arterioles has been replaced by two smaller decreases in pressure arranged in series: one (now lower) at the arterioles and a new one at the stenosis. Second, the remaining arteriolar vasomotion can be tested by a transient total occlusion. Release of the occlusion normally is followed by a temporary hyperemia as evidence of coronary arteriolar dilation provoked by the occlusion.

A moderate stenosis does not decrease coronary blood flow at rest but does diminish the magnitude of the postocclusion hyperemia, revealing that the arteriolar dilation responsible for postocclusion hyperemia was used in adjusting to the stenosis. By the time progressive increments in severity of the stenosis finally cause an appreciable reduction in resting coronary flow (75 to 85 percent decrease in luminal diameter), postocclusion hyperemia is virtually abolished.[17,18] From that point, further narrowing causes a proportional reduction in coronary blood flow. It seems probable that the arteriolar dilatation used to compensate for coronary arterial stenosis at rest is the same arteriolar dilatation normally kept in reserve to meet augmented blood flow requirements during periods of increased cardiac activity, and that the reserve is practically exhausted before a decrease in resting blood flow occurs. Coronary collateral development represents a different type of vascular compensation to focal ischemia, and will not be discussed here.

These data obtained from animal experiments are consistent with clinical and laboratory features of patients with chronic coronary artery disease. Most are asymptomatic at rest. As long as they have not had a previous myocardial infarction, the mechanical function of their heart often appears normal, and most estimates of coronary blood flow are within the normal range despite the presence of severe obstruction involving arteries supplying viable myocardium.

Whether hypoperfusion over an extended period is ever compatible with viability of heart muscle is an important unresolved question. One approach to this question is to examine the coronary venous blood for evidence of myocardial anaerobic glycosis. In our experience, lactate is consistently absorbed from the blood by the myocardium and oxidized in patients with normal coronary circulation. Lactate extraction of less than 10 percent or net lactate production by the heart is abnormal and seems to be a rather specific sign of myocardial hypoxia.[4] In about 7 percent of the patients with coronary heart disease whom we have tested lactate extraction at rest has been abnormal.[4] The prevalence rate has been about the same for patients with chronic or unstable angina. We wondered if these occasional instances of abnormality at rest might be a sign that coronary artery disease caused myocardial oxygen supply to fluctuate, and that we were observing random isolated instances of hypoxia, which were asymptomatic and without sequelae because of their transient pattern. We have had occasion to evaluate this hypothesis by reexamining a sizable number of patients routinely as a part of prospective research protocols. Eight of these patients exhibited abnormal lactate extraction at rest on their initial examination. We were surprised to discover that the same abnormality was present in five of the eight patients when they were reexamined after an average interval of 6 months. These results raise the possibility that exceptional patients may have chronic myocardial hypoxia at rest for rather long periods.

Relative ischemia during acute stress: The concept described here is that coronary ischemia during increased cardiac activity in patients with coronary heart disease is due to exhausted coronary reserve. Coronary blood flow increases as long as further arteriolar dilation is possible, but maximal coronary blood flow is subnormal because of interposed atherosclerotic resistance in the large arteries. Clinical physiologic observations are consistent with this scheme. When the heart rate of patients with chronic coronary heart disease is increased in steps by atrial pacing, coronary sinus blood flow increases until angina occurs, and then blood flow does not increase further.[19] Decrease in lactate extraction by the heart or reversal from net uptake to net lactate production, although unusual in patients with coronary artery disease when they are at rest, commonly occurs during atrial pacing[20,21] (Fig. 2). Thus, coronary blood flow is adequate for resting needs, but cannot meet the increased metabolic demands of the

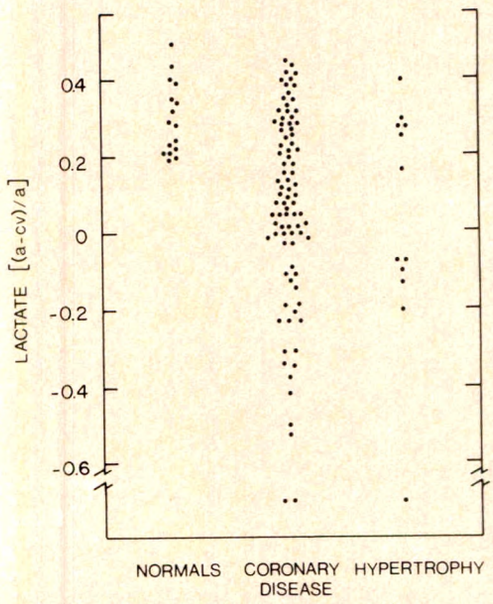

FIGURE 2. Lactate extraction by the myocardium ([arterial − coronary venous]/arterial [a − cv/a]) during atrial pacing (heart rates 100 to 140 min^{-1}) in normal subjects, patients with symptomatic coronary heart disease and patients with left ventricular hypertrophy associated with aortic stenosis. Each **dot** represents one patient. Values below 0.1 or negative values indicate abnormally reduced extraction or lactate production by the myocardium, as a sign of anaerobic glycolysis due to myocardial hypoxia. (Data from Neill and Kremkau[4] and Trenouth et al.[32])

heart during tachycardia. Myocardial mechanical dysfunction can also be brought about or made worse by atrial pacing or exercise,[22,23] as a further manifestation of the inability of the coronary circulation to keep up with rising needs of energy flow when the work of the heart increases beyond a critical point.

Transmural distribution of ischemia: Transmural coronary blood flow distribution in dogs remains normal in the resting state in the face of moderate coronary stenosis (Fig. 1.) However, because reserve vasodilatation is utilized to compensate for the stenosis, the subendocardium becomes progressively vulnerable to other superimposed hemodynamic changes that compromise diastolic blood flow and that require further subendocardial arteriolar dilation to maintain perfusion. Tachycardia provoked by pacing[24,25] or exercise[26] then causes subendocardial ischemia in the region of the heart supplied by the stenosed artery (Fig. 1). Coronary blood flow needs are increased throughout the left ventricle, but by encroaching on diastolic time, the tachycardia interferes with perfusion to a much greater extent in the subendocardial layer. Subendocardial ischemia in the region of coronary obstruction also is accentuated by an increase in diastolic tissue pressure and extravascular compression such as that produced by blood volume expansion.[16]

Further increments in coronary arterial narrowing eventually cause ischemia at rest as well, first in the subendocardium and only with severe stenosis in the subepicardium.[27] Acute complete coronary occlusion in the dog causes transmural ischemia that is more severe in the subendocardial layer.[28] Even with a low heart rate, coronary reserve seems to be exhausted first in the subendocardium. The explanation is not entirely clear because coronary arteriolar reserve as assessed by maximal vasodilatation seems to be essentially uniform transmurally. Increasing diastolic extravascular compression due to increased ventricular volume, incomplete relaxation or tissue edema may be a contributing factor. These experimental results in dogs coincide with electrocardiographic evidence that reversible ischemia during exercise is primarily subendocardial and with pathologic findings of relatively extensive subendocardial necrosis in myocardial infarction.

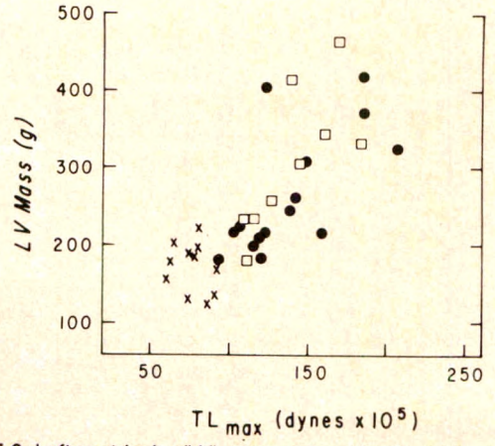

FIGURE 3. Left ventricular (LV) mass and maximal total load (TL_{max}) during contraction ($r = 0.79$). **Crosses** indicate normal subjects; **closed circles** indicate patients with aortic stenosis and **open squares** indicate patients with aortic insufficiency. (Reproduced from Trenouth et al.,[32] with permission.)

Cardiac Work Hypertrophy

Special case of intermittent repetitive exercise: The coronary vascular response to intermittent exercise parallels the temporary increase in cardiac activity as already mentioned. Physiologic indexes return to baseline during sedentary intervals. However, a sufficient intensity of intermittent exercise provokes permanent changes, including growth of myocardium and coronary blood vessels.[28–30] The maximal capacity of the heart for work, oxygen consumption and coronary blood flow increases to above normal levels.[31] This is a special type of cardiac adaptation to stress in which the work requirements per unit of myocardial mass (or sarcomere) presumably become less than normal during sedentary intervals. Also, requirements for coronary blood flow at rest must be small relative to the enlarged capability of the coronary circulation. There is no reason to suspect that this form of myocardial hypertrophy would compromise its oxygen supply. The magnitude of hypertrophy that occurs with exercise training is relatively small, and coronary functional capacity seems to be proportionately augmented.

Energy turnover per gram in pathologic hypertrophy: A sustained increase in cardiac work leads to marked hypertrophy, involving both contractile work elements and energy turnover mitochondrial elements. Figure 3 illustrates the relation between left ventricular mass and total force generated by the left ventricle that we found in a group of normal subjects and patients with chronic stenosis or incompetence of the aortic valve. The observations were made with the patients at rest. The mass of the left ventricle was greatly increased in the patients with aortic valve disease. Myocardial mass remained proportional to the force of contraction over a very broad range. A similar relation was observed between total coronary blood flow or myocardial oxygen consumption and total left ventricular force.[32] Although the enlarged left ventricle performs an enormous amount of work, the left ventricular wall stress (force per cross-sectional area)[33] as well as oxygen consumption and coronary blood flow per gram of myocardium are near normal.[32,34] These data imply that when the heart confronts a chronic work overload, the growth of cardiac muscle is regulated in some fashion to maintain work performed, energy turnover and blood supply to each contractile unit within normal limits in the resting state.

Coronary microcirculation: Although the minute volume of nutritional blood flow to the heart keeps pace quantitatively with the hypertrophy, at least when the patient is at rest, the microcirculation apparently does not. Microscopic examination of hypertrophied hearts removed from human beings[35] and, more recently, photomicrographs made of beating perfused hypertrophied rat hearts[36] have demonstrated a slight increase in intercapillary distances. If the diffusion distance to its destination is farther, the concentration

gradient for oxygen must expand to maintain the same rate of oxygen flow. Thus, if intercapillary distances are increased in hypertrophied hearts, the normal coronary venous blood PO_2 and oxygen consumption per gram of myocardium implies low PO_2 at the mitochondria in patients with aortic valve disease. Moreover, the photomicrographs in rats indicate that the normal small reserve of unperfused capillaries is partly spent in hypertrophied hearts even under basal conditions. The status of the microcirculation has also been investigated by determining resistance to coronary blood flow in hypertrophied dog hearts during pharmacologically provoked maximal vasodilatation.

Expressed per gram of myocardial tissue, maximal coronary blood flow is reduced and minimal coronary vascular resistance is increased in hypertrophied hearts.[37,38] If the total number of arterioles is somewhat greater in the hypertrophied heart, at least the increase is not in proportion to the increased muscle mass. Each arteriole must supply a greater than normal amount of tissue, and the normal blood flow per gram would have to be achieved by arteriolar dilation, probably at the expense of coronary reserve. The widened intercapillary distance raises some doubts about the adequacy of nutritional blood supply to the hypertrophied heart even under basal resting conditions, and the utilization of arteriolar (and perhaps also capillary) reserve at rest can be expected to limit further increase in coronary blood flow needed during superimposed acute stress.

Relative ischemia during acute stress: Patients with chronic aortic valve disease, particularly those with aortic stenosis, frequently experience exertional chest pain even if they have normal coronary arteries. Lactate extraction by the myocardium was normal at rest in patients with aortic stenosis or insufficiency whom we evaluated during cardiac catheterization, although these observations do not rule out a possible role of myocardial hypoxia in aortic valve disease in patients acutely ill with severe heart failure. Tachycardia induced by atrial pacing frequently provoked myocardial lactate production in patients with aortic stenosis[32,39] (Fig. 2). Similar evidence of myocardial hypoxia during tachycardia was not found in patients with aortic insufficiency despite a comparable degree of left ventricular hypertrophy.[32] These data indicate that although myocardial oxygen supply seemed to be compensated with the patient at rest, the remaining coronary reserve, at least with aortic stenosis, was incapable of meeting the additional temporary increase in metabolic requirements during tachycardia. As in patients with obstructive coronary disease, the exertional chest pain seems to be related to reversible myocardial ischemia.

The role of myocardial hypoxia as a basis for myocardial dysfunction in left ventricular hypertrophy remains to be clarified. The results of lactate extraction during tachycardia show that myocardial oxygen supply is compromised in patients with aortic stenosis to the extent that episodes of myocardial hypoxia probably occur rather often during the course of ordinary physical activity. We do not know whether such episodes of apparently reversible hypoxia exert a permanent deleterious effect on myocardial function or are related to the intramyocardial fibrosis[40] that may occur in these patients.

Transmural distribution of ischemia: Subendocardial perfusion in patients with aortic valve disease is jeopardized partly by the ventricular hypertrophy and partly by the hemodynamic accompaniments of abnormal valve function. Either stenosis or insufficiency of the aortic valve results in left ventricular systolic pressure that is high relative to diastolic aortic pressure. The high ventricular systolic pressure increases coronary blood flow requirements; the low diastolic pressure impairs perfusion. Despite compensatory coronary arteriolar dilation, which may succeed in preventing diffuse ischemia, the pattern of myocardial perfusion is disturbed. When aortic insufficiency is created acutely in dogs, coronary blood flow shifts mainly to the systolic phase of the cardiac cycle. The reduced diastolic pressure is unable to sustain normal blood flow during diastole, which is the period responsible for most of the subendocardial perfusion.[41]

The effect of relatively increased systolic and decreased diastolic aortic pressure on transmural blood flow distribution has been investigated in open chest dogs by narrowing their ascending aorta (proximal aortic pressure 200/100 mm Hg) or opening a large systemic arteriovenous fistula (aortic pressure 100/40 mm Hg).[42] Subendocardial ischemia developed in these dogs (the results may have been provoked partly by the very high heart rates). In another investigation, moderate stenosis in the aortic valve position was created, and myocardial tissue lactate concentration as well as lactate and oxygen extraction from the coronary blood were determined.[43] Tachycardia induced by administration of isoproterenol resulted in increased myocardial lactate concentration in the subendocardium and lactate output into the coronary venous blood. The results of these experiments in dogs help to form the concept of ischemia in left ventricular hypertrophy associated with aortic valve disease (Fig. 1). Coronary blood flow to the muscle is compensated at rest by arteriolar dilation, more marked in the subendocardium because of high extravascular compression relative to coronary perfusion pressure. With tachycardia, increased coronary blood flow needs and decreased diastolic perfusion time apparently exceed coronary arteriolar reserve initially in the subendocardium, resulting in diffuse subendocardial hypoxia and anaerobic glycolysis with lactate output into the coronary venous blood.

Unified Interpretation of the Chemical Signs of Myocardial Hypoxia in Patients

Myocardial lactate production as a marker of myocardial hypoxia and ischemia: Estimation of myocardial lactate extraction from samples of arterial and coronary sinus blood obtained during atrial pacing[20,21] has been the standard method for demonstrating chemically the presence of ischemic myocardial hypoxia in patients. Lactate production or abnormally low lactate extraction often occurs in patients with coronary artery disease. However, lactate extraction remains normal in some patients during tachycardia,

even in those patients with typical angina pectoris. Normal myocardial lactate extraction during angina in patients with documented obstructive coronary disease is most likely due to blood sampling difficulties, that is, inaccessibility of the coronary sinus catheter to the coronary venous blood draining a localized region of ischemic myocardium. Normal lactate extraction is especially common in patients with isolated right coronary artery disease, which would be expected to involve myocardium that does not contribute venous blood to the coronary sinus at the usual sampling site.[4,44] There is another apparent inconsistency in the coronary venous blood chemical values accompanying angina, which has received surprisingly little comment: Increased lactate concentration in coronary venous blood, when it does occur, is usually not accompanied by a corresponding decrease in coronary venous blood PO_2, as might be expected with tissue hypoxia due to low blood flow. We believe that this phenomenon, rather than representing focal coronary artery disease, is a rather specific sign of subendocardial hypoxia associated with redistribution of blood flow preferentially into the relatively well oxygenated subepicardial layers.

Myocardial hypoxia during tachycardia: A large number of values for myocardial lactate extraction and coronary venous blood PO_2, obtained from different types of patients, are analyzed in Figure 4. Lactate extraction remained normal during tachycardia in patients with normal coronary arteries (Fig. 4, left panel) but decreased when heart rate was increased in patients with coronary artery disease (center panel). Coronary venous blood PO_2 on the average actually increased slightly during tachycardia not only in the normal subjects but also to a similar degree in the patients with coronary artery disease, more than half of whom were experiencing chest pain at the time. We pointed out earlier in this article that tachycardia in dogs with or without coronary stenosis redistributes blood across the left ventricular wall so that a greater fraction of the blood traverses the subepicardium where the PO_2 is increased. One would expect this redistribution of blood flow to increase the PO_2 of the mixed coronary venous blood, a result that could explain the findings in the normal human beings.

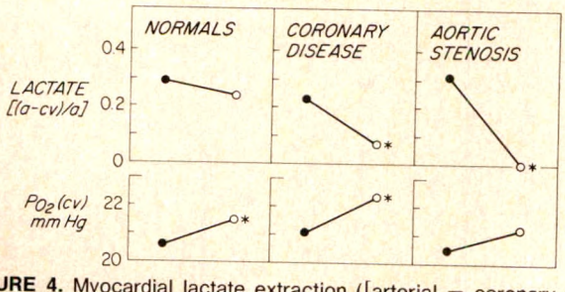

FIGURE 4. Myocardial lactate extraction ([arterial − coronary venous]/arterial [a − cv/a]) and coronary venous (cv) blood PO_2 in 12 normal subjects, 24 patients with coronary heart disease and 12 patients with aortic stenosis and normal coronary arteries. **Lines** connect mean values at rest (**solid symbols**) with mean values during tachycardia induced by atrial pacing (**open symbols**). **Asterisk** indicates values during tachycardia different from those at rest, $P < 0.01$. (Data from Neill and Kremkau[4] and Trenouth et al.[32])

In the patients with coronary disease, when perfusion of the heart fails to increase normally during tachycardia, myocardial and coronary venous blood PO_2 would be expected to decrease, as in fact it does in some patients. However, if the ischemia was confined to the subendocardial layer or was much more intense in this area, as found in the experiments in dogs, venous blood issuing from the hypoxic subendocardium would contribute only a relatively small portion to the total volume of mixed coronary venous blood. The more intense the subendocardial ischemia, the smaller the contribution. The same mixing phenomenon will tend to obscure the increase in subendocardial lactate concentration, but there is an important difference. Although PO_2 cannot fall below 0, tissue lactate concentrations under hypoxic conditions can rise several-fold. Therefore, a very small volume of venous blood from intensely ischemic subendocardium mixed with a larger volume of venous blood from relatively well perfused and oxygenated subepicardium could produce an easily detectable increase in coronary sinus lactate concentration with no change or even an increase in coronary sinus PO_2.

Myocardial ischemia in left ventricular hypertrophy: Examination of patients with myocardial ischemia related to diffuse left ventricular hypertrophy should provide a test of focal coronary disease versus subendocardial ischemia as an explanation for the changes observed in lactate extraction and coronary venous blood PO_2. Data for patients with aortic stenosis and left ventricular hypertrophy but no significant coronary artery disease are shown in Figure 4, right panel. Abnormal lactate extraction in these patients was also accompanied by a slight increase in coronary venous blood PO_2. These data conform closely to the results in dogs with aortic stenosis in which hypoxia and lactate production in the subendocardium were accompanied by an increase in coronary venous blood lactate concentration without a decrease in coronary venous blood PO_2.[43]

Unified concept of subendocardial ischemia and angina: The data presented in Figure 4 are consistent with a unified interpretation. They suggest that angina pectoris induced by tachycardia, whether in patients with focal coronary artery disease or patients with aortic stenosis, is typically associated with subendocardial ischemia—probably heterogeneous in the former patients and diffuse in the latter. Transmural ischemia, if it is manifested as we suggest by a decrease in coronary venous blood PO_2, is uncommmon when tachycardia is induced in patients by atrial pacing. The S-T segment depression that occurs when angina is induced by exercise in the same types of patients ordinarily is interpreted as a sign that the ischemia is subendocardial. Thus, the chemical data obtained during pacing and the electrocardiographic data during exercise tend to corroborate each other, suggesting that the subendocardium is the typical location of reversible ischemia in patients.

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Serial Echocardiographic Appearance of Healing Bacterial Vegetations

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Serial M mode and cross-sectional echocardiograms were obtained from six patients who had been treated with antibiotic drugs for infectious endocarditis. Three to six M mode echocardiograms and one to six cross-sectional echocardiograms were obtained from each patient over a follow-up period averaging 50 weeks (range 10 to 108 weeks). On echocardiography, vegetations were observed to have become smaller and more echo-reflective with healing. A dramatic change was seen in two patients after peripheral embolization. M mode echocardiography was particularly helpful in determining the quality of echo reflection by vegetations; cross-sectional echocardiography was more helpful in judging the size and shape of a vegetation. Echocardiography is ideally suited for the serial visualization of healing vegetations in patients who do not require early valve replacement. It may prove helpful to examine serially valve vegetations with both M mode and cross-sectional echocardiography when following up patients with infectious endocarditis treated with antibiotic agents.

The direct, noninvasive visualization of valve vegetations has been an exciting new development in the evaluation of patients with infectious endocarditis.[1-9] Vegetations are identified in the M mode echocardiogram as coarse irregular echoes that are attached to valve leaflets but do not significantly impair their motion. More recently, cross-sectional echocardiography has been used to visualize vegetations in two dimensions.[10,11] The improved spatial orientation provided by cross-sectional echocardiography may permit better estimation of the size, shape and mobility of a vegetation.

Although changes in the M mode echocardiographic appearance of valve vegetations after antibiotic therapy have been reported,[12] we have previously been unable to detect these changes,[8] perhaps because most of our patients with vegetations detected on M mode echocardiography required early valve replacement for intractable heart failure. The length of follow-up in these patients may not have been sufficient to detect changes associated with healing. However, several of our patients with vegetations detectable on echocardiography have survived for long periods of time without requiring valve replacement. Additionally, more recent echocardiographic examinations have included cross-sectional studies as well as M mode echocardiography. It has been suggested that cross-sectional echocardiography may be particularly well suited to the detection of morphologic change in a vegetation after treatment.[11] This investigation was therefore undertaken to examine the serial M mode and cross-sectional echocardiographic appearances of valve vegetations in patients surviving for long periods of time with infectious endocarditis treated with antibiotic agents.

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Methods

Patients: Clinical records and echocardiograms were reviewed from all patients who (1) had a clinical diagnosis of infectious endocarditis based on the presence of fever, an organic heart murmur and positive blood cultures; (2) had valve vegetations detected on M mode and cross-sectional echocardiography, and (3) were available for serial clinical and echocardiographic examinations for at least 10 weeks after initial presentation without intervening valve replacement. Of 23 patients with endocarditis examined with both M mode and cross-sectional echocardiography in our laboratories, 6 patients met these criteria. Four patients were men, and two were women; their ages ranged from 21 to 63 years (average 37.5 years). Endocarditis was caused by Streptococcus sanguis in two patients, Staphylococcus aureus in two patients, alpha hemolytic streptococcus in one patient and Streptococcus bovis in one patient. Two patients had aortic vegetations, two mitral, one tricuspid and one both aortic and mitral. Three to six M mode echocardiograms and one to six cross-sectional echocardiograms were obtained from each patient during the follow-up period, which averaged 49.6 weeks (range 10 to 108 weeks).

Echocardiography: M mode echocardiograms were performed with a commercially available ultrasonoscope (Smith-Kline Instruments, Inc., Sunnyvale, California) and a 2.25 megahertz piezoelectric transducer focused at 7.5 cm. Examinations were recorded on light-sensitive paper using a strip chart recorder. Cross-sectional echocardiograms were performed with a 30° mechanical sector scanner (Smith Kline Instruments), and recorded on videotape for analysis in real time, slow motion and stop frame formats. Standard techniques were used in performing both the M mode and cross-sectional examinations. An attempt was made to visualize the vegetations from all available echocardiographic windows. The echocardiograms were analyzed by two independent observers who had no knowledge of the clinical course of the individual patients or the temporal sequence in which the echocardiographic examinations were performed.

The echocardiographic diagnosis of a vegetation was based on the presence of a mass attached to a valve leaflet that did not significantly impair movement of the leaflet. The size, shape, mobility and overall appearance of a vegetation were estimated by qualitative review of the cross-sectional echocardiographic videotapes. M mode echocardiograms were similarly reviewed for the presence and location of vegetations. The density of echo reflection by a vegetation was estimated by comparing the appearance of a vegetation with other structures recorded in the same study because precise gain settings may have varied in serial studies. After analysis of the echocardiograms, the serial echocardiographic appearances of the vegetations were compared with the patients' clinical features.

Results

Case 1: A pregnant 35 year old woman with a history of mild aortic regurgitation entered the hospital after the sudden onset of right hemiparesis. She had noted low grade fever for 3 weeks before admission. Examination revealed mild right hemiparesis, ataxia and a diastolic decrescendo murmur. Blood cultures grew Streptococcus sanguis. Antibiotic agents were administered and the patient's fever abated and she remained in stable condition both neurologically and hemodynamically. M mode and cross-sectional echocardiograms obtained on the day of admission and 16 days later showed a vegetation attached to the aortic valve. A representative section of the M mode echocardiogram obtained on day 1 is shown in Figure 1A. Selected systolic and diastolic frames of the cross-sectional echocardiogram performed on day 16 are shown in Figure 2A.

In the cross-sectional echocardiogram, the vegetation appeared pedunculated, and prolapsed freely into the left ventricular outflow tract during diastole. On M mode echocardiography, the characteristic coarse irregular echoes of a vegetation could be seen attached to the aortic valve. In addition, parts of the valve apparatus exhibited high frequency diastolic fluttering, suggesting fenestration of the leaflets.[6] Scanning of the left ventricular outflow tract revealed that part of the vegetation or valve apparatus extended into the left ventricular outflow tract, lying over the anterior mitral valve leaflet during diastole. Neither the M mode nor the cross-sectional echocardiogram changed appreciably between admission and day 16 of treatment, despite apparently effective antibiotic therapy.

Twenty-nine days after admission, the patient suddenly became semicomatose. A brain scan showed multiple filling defects. A repeat cross-sectional echocardiogram (Fig. 2B) again showed a large mass attached to the aortic valve, but the vegetation was distinctly smaller, and no longer prolapsed as freely into the left ventricular outflow tract. A healthy infant was delivered by cesarean section the day after onset of coma. The patient remained afebrile, continued to be hemodynamically stable and gradually regained neurologic function.

A repeat M mode echocardiogram after the stroke (Fig. 1B) continued to show a vegetation attached to the aortic valve, but abnormal echoes were no longer present in the left ventricular outflow tract. A repeat cross-sectional echocardiogram obtained 55 days after admission (Fig. 2C) showed the vegetation to be slightly smaller in size. Repeat echocardiograms obtained 87 days, 14 months and 2 years, respectively, after presentation showed a small echo-dense mass attached to the aortic valve. Representative examples of these M mode and cross-sectional echocardiograms are shown in Figures 1C and 2D. No appreciable change in the appearance of the aortic valve was observed on either M mode or cross-sectional echocardiography on these three long-term follow-up studies. The patient continues to have moderately severe aortic regurgitation, but the left ventricle has not dilated, and she is free of cardiovascular symptoms. She has had a dramatic return of neurologic function, and now has only mild speech impairment.

Case 2: After a tooth extraction a 31 year old man had fever, a murmur of aortic regurgitation and Staphyloccocus aureus bacteremia. He was admitted with a left popliteal arterial embolus. M mode and cross-sectional echocardiograms on admission showed very large nonmobile vegetations attached to the aortic valve, and diastolic fluttering of the valve leaflets consistent with fenestration. After 4 weeks of antibiotic therapy, the patient discharged himself from the hospital. He returned 2 weeks later in a semicomatose state with presumed brainstem emboli.

A repeat M mode echocardiogram at that time was essentially unchanged but a cross-sectional echocardiogram showed the vegetation to be definitely smaller in size. The patient's condition gradually improved with medical therapy and he has been followed up for a total of 180 days. Serial M mode echocardiograms have shown little change in the vegetation itself, but the left ventricle has gradually dilated. Cross-sectional echocardiograms showed that the vegetation slowly became smaller. The patient has regained near normal neurologic function but is limited by exertional dyspnea and fatigue. Elective aortic valve replacement is planned.

Case 3: Immediately before presentation, a 48 year old man with chronic glomerulonephritis had resumed long-term maintenance with hemodialysis after rejection of a cadaveric renal transplant. He presented with purulent drainage from his surgical incision, fever, a holosystolic murmur and Staphylococcus aureus bacteremia. M mode and cross-sectional echocardiograms (Fig. 3, A and B) showed a moderate-sized vegetation attached to the posterior mitral leaflet. Repeat cross-sectional echocardiograms 30 and 78 days, respectively, after initiation of treatment showed that the vegetation had become smaller and more echo-reflective. No appreciable change in the size of the vegetation was noted on M mode echocardiography, but the mass did appear to become more echo-reflective. Left ventricular and left atrial dimen-

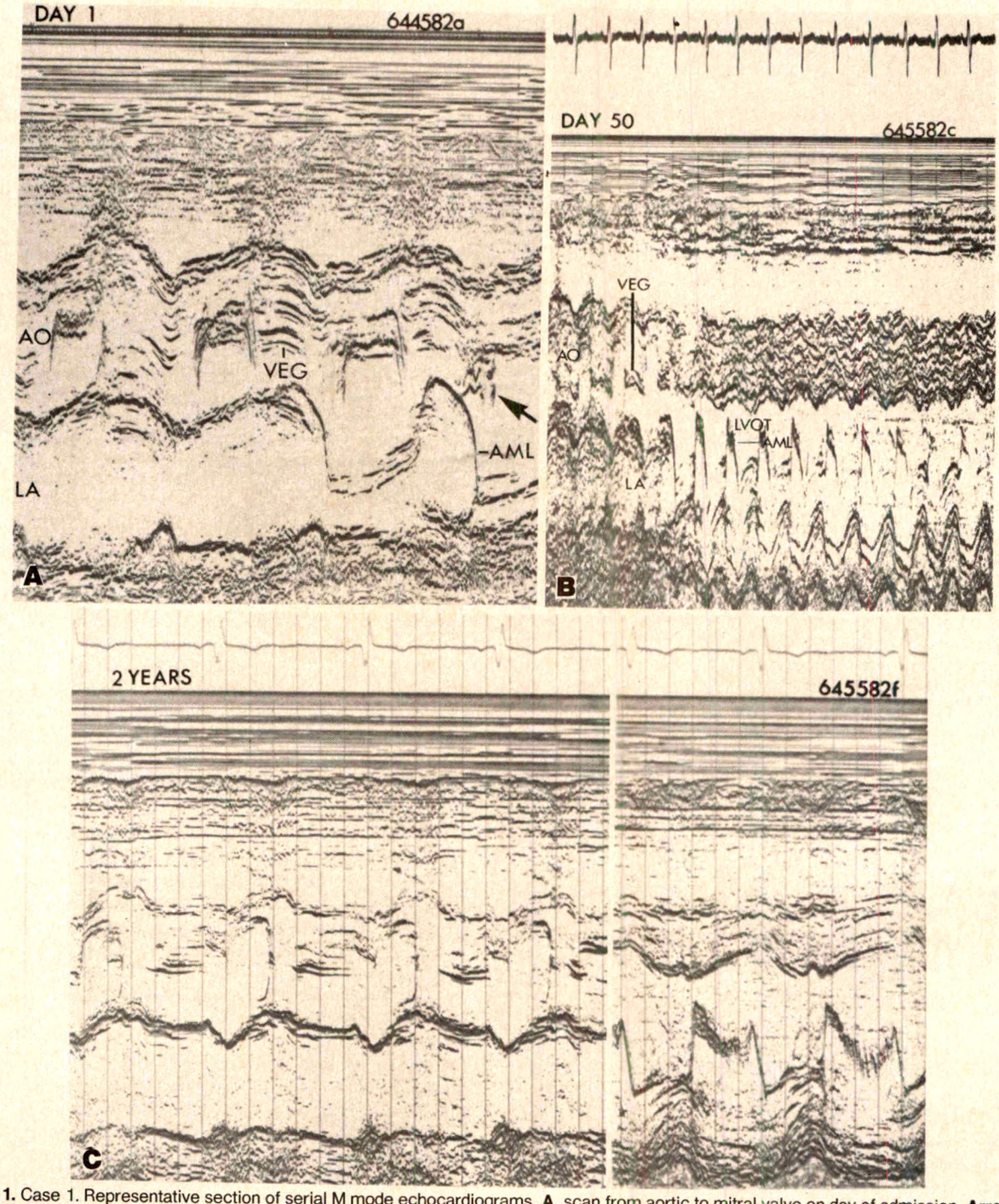

FIGURE 1. Case 1. Representative section of serial M mode echocardiograms. **A,** scan from aortic to mitral valve on day of admission. **Arrow** points to vegetation (VEG) prolapsing into left ventricle overlying anterior mitral leaflet during diastole. AML = anterior mitral leaflet; AO = aorta; LA = left atrium. **B,** scan from aortic to mitral valve 50 days after admission, after cerebral embolization. The vegetation no longer prolapses into the left ventricular outlfow tract (LVOT). **C,** aortic (**left**) and mitral (**right**) valve echograms obtained 2 years after presentation. There is thickening of the aortic valve representing residual change in the valve after endocarditis. The anterior mitral valve leaflet flutters during diastole because of aortic regurgitation.

sions were stable. The patient now has no cardiac symptoms.

Case 4: A 27 year old man had previously undergone total surgical repair for tetralogy of Fallot. He presented with fever, petechiae and a holosystolic murmur. Alpha hemolytic streptococci were cultured from his blood, and he was successfully treated with antibiotic drugs. Echocardiograms on admission showed a moderate-sized nonmobile vegetation attached to the anterior mitral leaflet. Repeat cross-sectional echocardiograms 10 and 44 weeks, respectively, after admission showed a gradual decrease in the size of the vegetation. M mode echocardiograms were not appreciably changed.

Case 5: A 21 year old woman, a drug abuser, presented with Staphylococcus aureus bacteremia and septic pulmonary emboli. The cross-sectional echocardiogram on admission (Fig. 4A) showed a smaller vegetation attached to the tricuspid valve. The M mode echocardiogram on admission (Fig. 4B) showed coarse irregular echoes attached to the anterior mitral leaflet. The patient was treated with antibiotic drugs and her condition gradually defervesced; serial chest X-ray films showed clearing. A repeat M mode echocardiogram 8 days after admission (Fig. 4B) was essentially unchanged, but 39 days after admission (Fig. 4B) the valve leaflet appeared essentially normal and did not change substantially on examinations performed 80 and 135 days after admission. A repeat cross-sectional echocardiogram 18 weeks after admission (Fig. 4A) showed no evidence of a vegetation.

Case 6: A 63 year old man presented with fever, murmurs of aortic and mitral regurgitation and Streptococcus bovis bacteriemia. M mode echocardiography showed vegetations attached to both the aortic and the mitral valves. A complete course of antibiotic therapy was administered. Aortic valve replacement was performed for severe aortic regurgitations 6 months later. Serial M mode echocardiograms over the next 2 years after aortic valve replacement showed no change in the size of the mitral vegetations. The valve appeared to become progressively more echo-reflective. The left ventricle and left atrium gradually dilated. A single cross-sectional echocardiographic study showed a thick, nonmobile echo-dense mass attached to the anterior mitral leaflet. Ninety-four weeks after

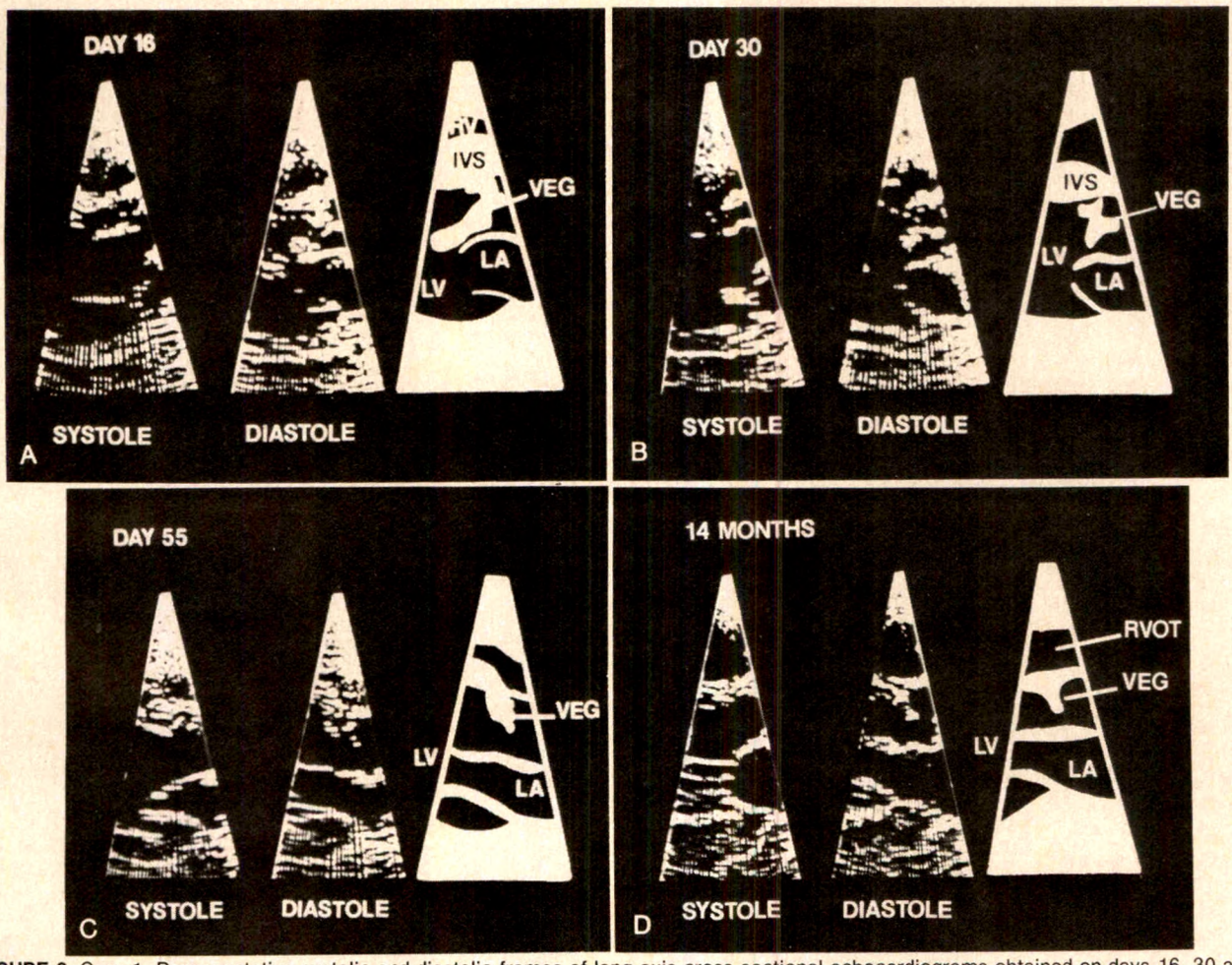

FIGURE 2. Case 1. Representative systolic and diastolic frames of long-axis cross-sectional echocardiograms obtained on days 16, 30 and 55 and 14 months after admission together with a labeled diagram corresponding to the diastolic frame. **A**, on day 16, a large pedunculated vegetation (VEG) attached to the aortic valve is seen prolapsing into the left ventricular outflow tract during diastole. IVS = interventricular septum; LV = left ventricle; RV = right ventricle. **B,** on day 30 (1 day after cerebral embolization), the vegetation no longer prolapses as far into the left ventricle. **C,** on day 55, the vegetation is still present but appears smaller. **D,** 14 months after admission, a small dense mass is still present on the aortic valve. No additional changes were noted on an additional echocardiogram (not illustrated) obtained 2 years after admission. RVOT = right ventricular outflow tract.

initial presentation, the patient underwent elective mitral valve replacement. Histologic examination of the mitral valve showed focal areas of hyalinization and calcification with chronic inflammatory cell infiltration.

Discussion

The formation of valve vegetations is a characteristic feature of infectious endocarditis. Osler[13,14] and many other investigators[15–21] have observed the morphologic appearance of vegetations at necropsy. Vegetations consist of platelet thrombi and clumps of bacteria or fungi coated with fibrin and erythrocytes. This mass is attached to a broad-based area of degenerated valve tissue. Vegetations assume a variety of shapes and sizes, and may appear flat and granular or elongated, fungating and friable. Vegetations may erode and disrupt the valve leaflets and adjacent structures. Pieces of vegetation may dislodge and result in peripheral embolization. Healing is initiated by the invasion of polymorphonuclear leukocytes and eventually the infecting organisms disappear. Fibroblasts infiltrate the area and the vegetation become hyalinized and may even calcify. The remnant of the vegetation is finally covered with a layer of endothelium.

Echocardiographic features of vegetations: With use of echocardiography it appears possible to observe certain of these pathologic changes in vivo. The valve vegetations were seen to diminish in size as they healed in all five patients studied with serial cross-sectional echocardiograms. Except in two patients with major peripheral embolization, this change in size was observed only after a relatively long period of time, commonly after completion of antibiotic therapy. Thus,

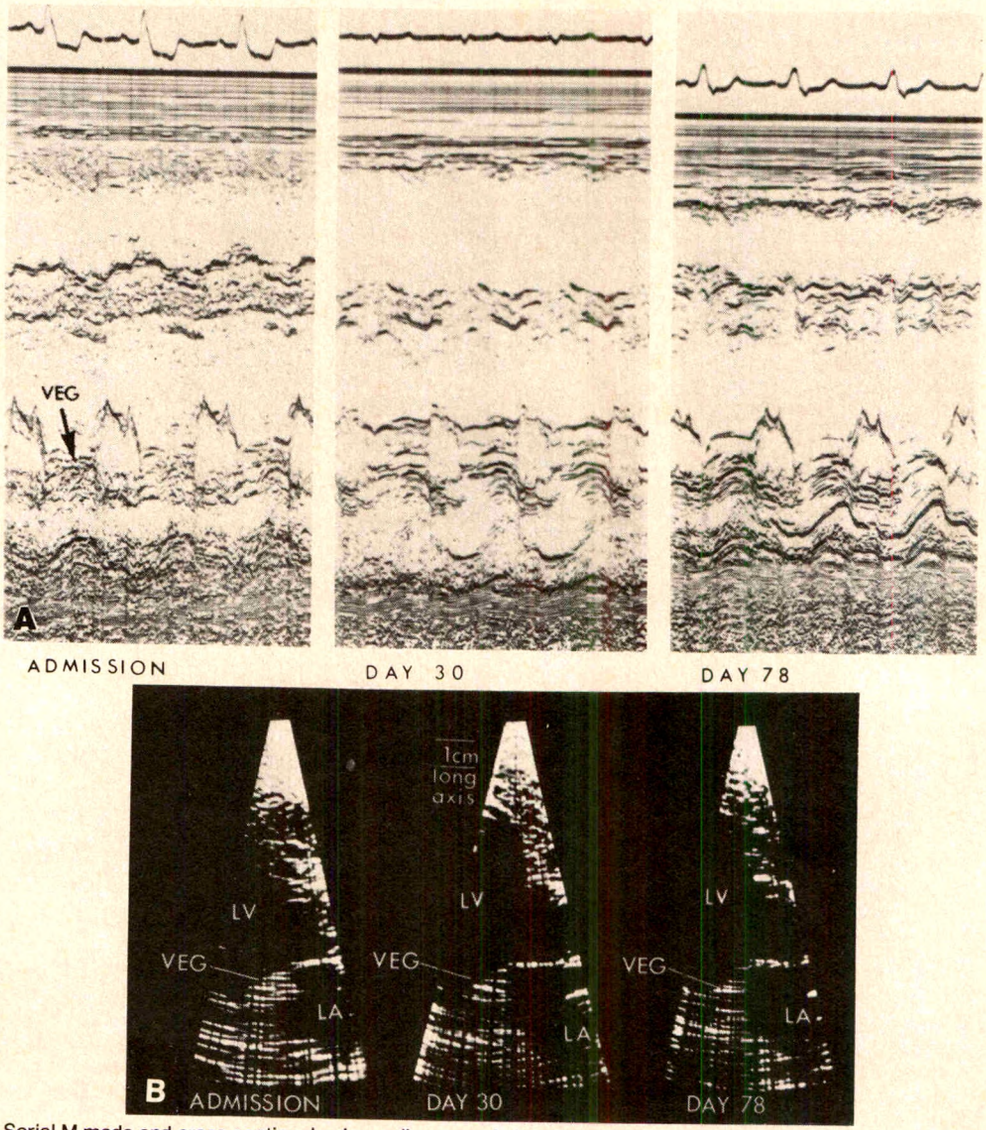

FIGURE 3. Case 3. Serial M mode and cross-sectional echocardiograms. **A,** M mode echocardiograms of the mitral valve obtained on day 1, 30 and 78 after presentation. No definite change in the size of the vegetation (VEG) can be appreciated, but the vegetation appears to reflect denser and more linear echoes on day 78 than on admission or on day 30. **B,** long-axis cross-sectional echocardiograms of the mitral valve show a vegetation (VEG) attached to the posterior mitral leaflet. The vegetation appears smaller on days 30 and 78. LA = left atrium; LV = left ventricle.

failure of a vegetation to become smaller during treatment did not indicate that treatment with antibiotic drugs was unsuccessful in these patients.

M mode echocardiography, which lacks true spatial orientation, was less helpful in detecting changes in the size of a vegetation, showing definite change in only two of the six patients serially studied. In four patients, the vegetations seemed to reflect ultrasound differently as healing progressed, appearing more echo-dense with time. This change in the acoustic property of a vegetation may be caused by hyalinization or calcification of the vegetation. The increase in specular reflection with healing was more readily appreciated on M mode echocardiography, which provided better grey-scale resolution than the cross-sectional echocardiographic system used.

Cross-sectional echocardiography showed an abrupt change in the appearance of the vegetations in two patients who had cerebral emboli. In one of these patients, an extremely mobile vegetation prolapsed freely into the left ventricular outflow tract before the patient's stroke. After the stroke, both M mode and cross-sectional echocardiograms showed that the vegetation no longer prolapsed as far into the left ventricular outflow tract during diastole. In the second patient, cross-sectional echocardiography showed that the very large nonmobile vegetation had become distinctly smaller immediately after embolization, although the M mode echocardiogram was not appreciably changed. Both of these patients with large cerebral emboli survived with antibiotic therapy and had only minimal long-term neurologic impairment.

Limitations of echocardiography: Changes in the structural characteristics of healing bacterial vegetations occurring over relatively long periods of time can be detected using a combination of M mode and cross-

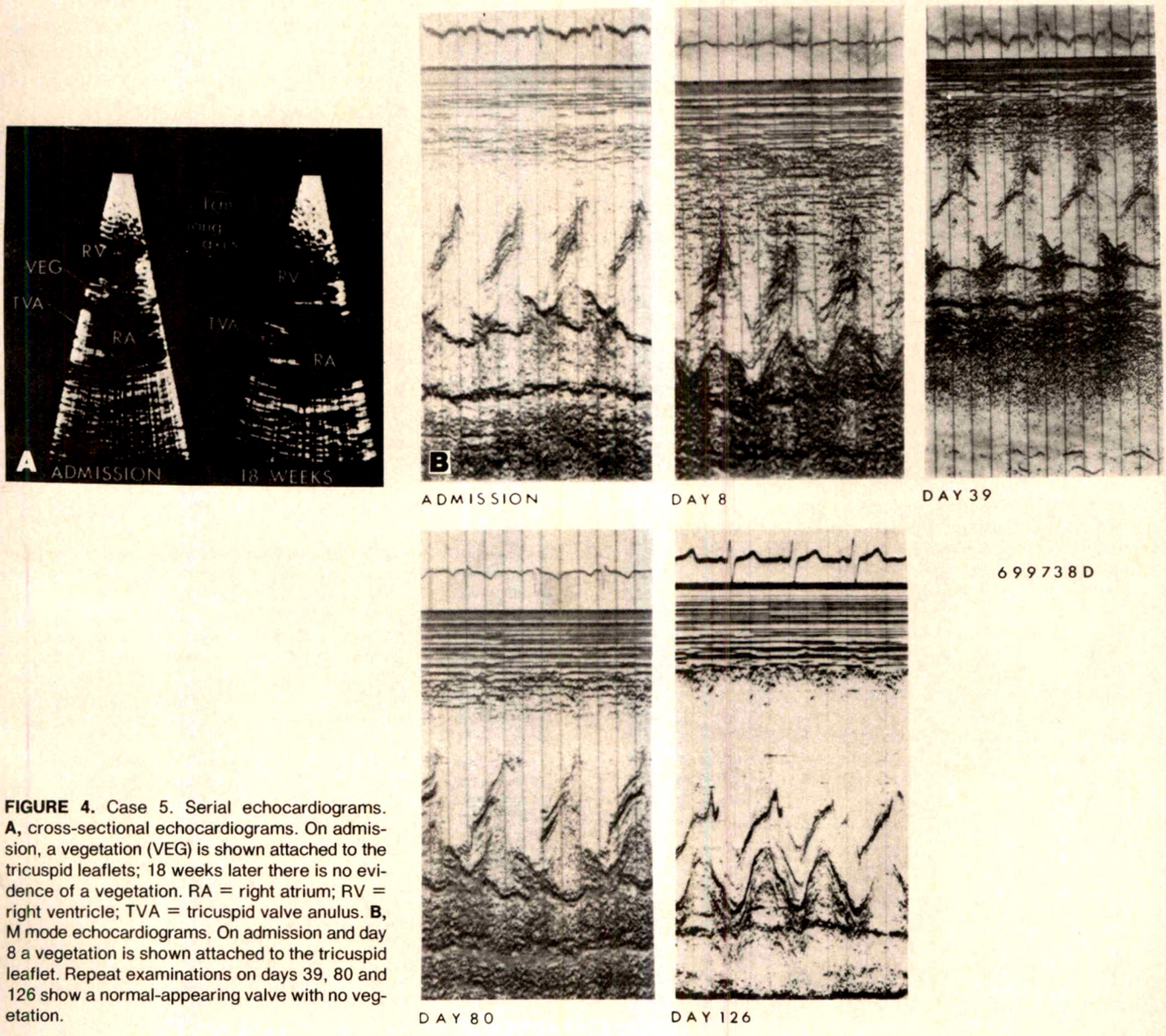

FIGURE 4. Case 5. Serial echocardiograms. **A,** cross-sectional echocardiograms. On admission, a vegetation (VEG) is shown attached to the tricuspid leaflets; 18 weeks later there is no evidence of a vegetation. RA = right atrium; RV = right ventricle; TVA = tricuspid valve anulus. **B,** M mode echocardiograms. On admission and day 8 a vegetation is shown attached to the tricuspid leaflet. Repeat examinations on days 39, 80 and 126 show a normal-appearing valve with no vegetation.

sectional echocardiography. Abrupt changes in a vegetation after embolization may also be detected. However, short-term changes in vegetations occurring during antibiotic therapy were not observed in our patients. At present, echocardiography probably does not have resolving power sufficient to appreciate small changes in vegetations occurring during treatment and cannot be used to judge antibiotic efficacy.

The lack of standardized gain settings and transducer positions also limits echocardiography as a technique for judging serial changes in valve vegetations. The M mode echocardiographic appearance of a vegetation may change dramatically with only minor changes in transducer position. The density of echo production by an intracardiac structure is directly dependent on the gain setting used. The serial density of a structure cannot be determined by direct comparison of subsequent echocardiograms unless the gain settings and transducer positions are identical, requirements that could not be met in this study. Thus, the density of echo-reflection by a given structure must be judged by comparing that structure with other structures within the same study at the same gain setting. Serial changes in echo-density can only be appreciated in a qualitative fashion.

The level of gain used is also important in determining the appearance of cross-sectional echocardiographic images, because the lateral resolution of this system is highly gain-dependent; as higher gain settings are used, lateral resolution decreases, causing intracardiac structures to appear larger. It is, therefore hazardous to compare the volume or cross-sectional area of a small structure such as a vegetation when measurements are made sequentially with different gain settings. However, it is possible to gain a qualitative appreciation of the change in size of a vegetation by viewing multiple real time sections of sequential echocardiograms performed at roughly equivalent gain settings.

Implications: Despite these limitations, echocardiography has tremendous potential in the evaluation of patients with endocarditis. Echocardiography is the only clinical tool currently available that is capable of directly visualizing valve vegetations during life, and it is well suited to the the performance of serial studies. As echocardiographic technology advances, it may be possible to visualize even smaller vegetations, observing more subtle changes in their morphologic features during treatment, and obtaining better quantitation of their acoustic properties.

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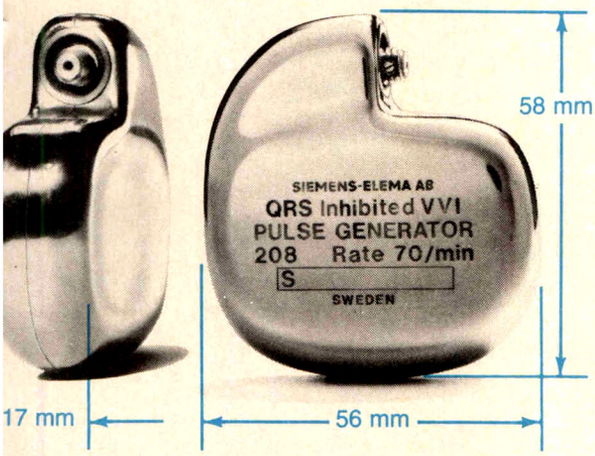

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- **Soft, convex-concave design.**
- **Hermetically sealed titanium encapsulation.**
- **Highly reliable hybrid circuitry.**
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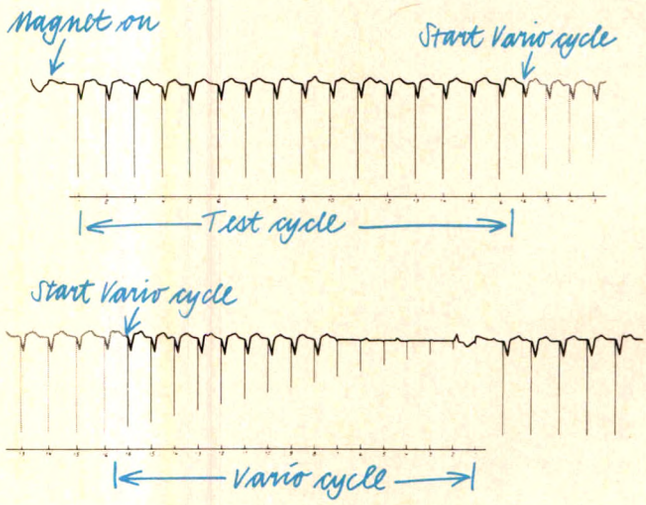

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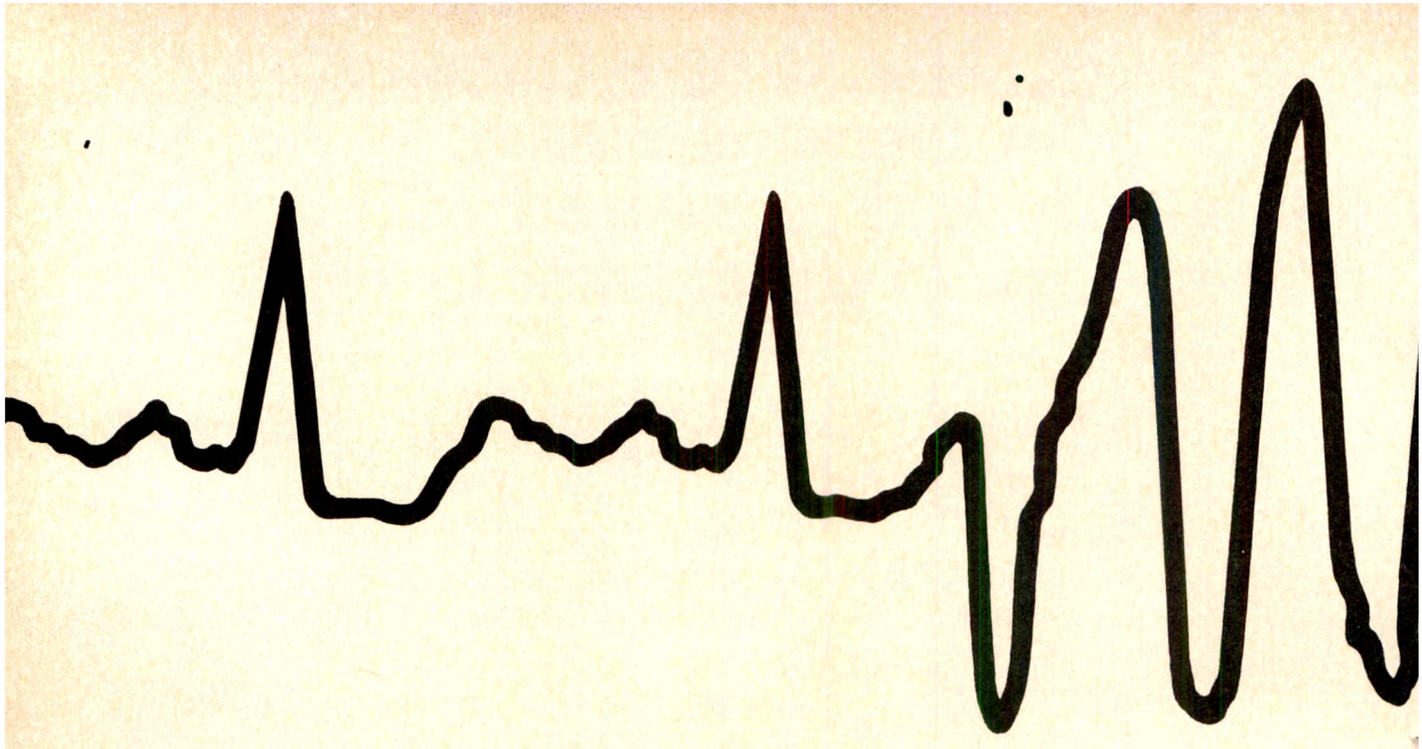

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Have they found an alternative to the error-prone, examiner-exhausting, rapid-fire Holter superimposition method?

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If you're not sure of the answers to all of these questions, we'll give them to you. No.

Now, we freely admit that we've stacked these questions to get the desired answer. But our point is that stacking them was far too easy to do.

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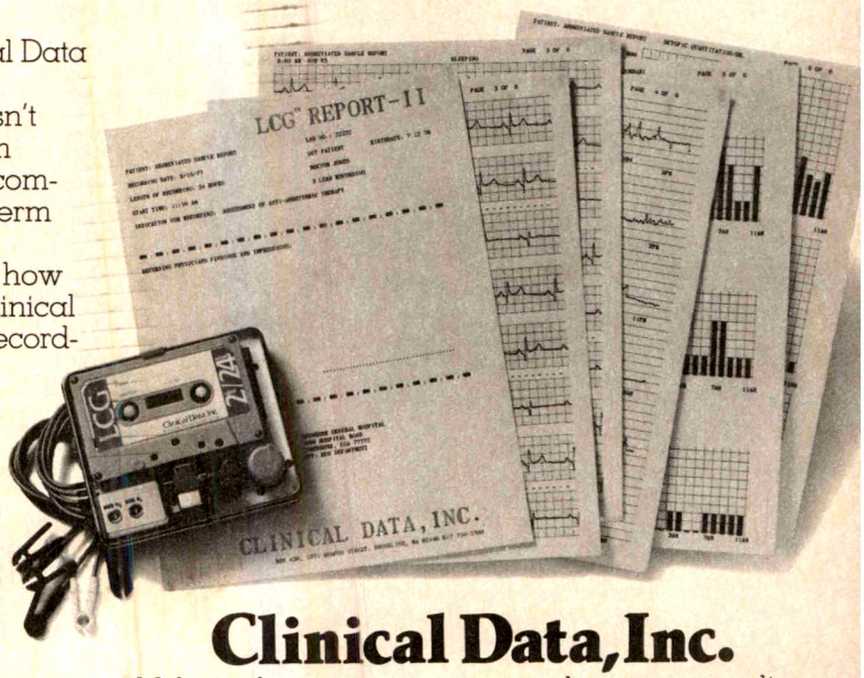
Is your long-term recording service really long-term?

new development introduced by Clinical Data over the last six years.

We feel strongly that any firm that hasn't made a similar commitment to long-term recording may not be a very long-term company. Or perhaps not worthy of a long-term commitment from you.

We'd like the opportunity to show you how all our competitive edges have made Clinical Data by far the largest long-term ECG recording service in the nation — with over fifty medically trained personnel examining hundreds of millions of heartbeats and preparing thousands of reports every month.

Send for our free brochure and sample LCG Report-II.™ It could be the beginning of a long-term relationship. Write to us at 1371 Beacon Street, Brookline, Massachusetts 02146. Or call toll free at 800-225-9180.



Clinical Data, Inc.

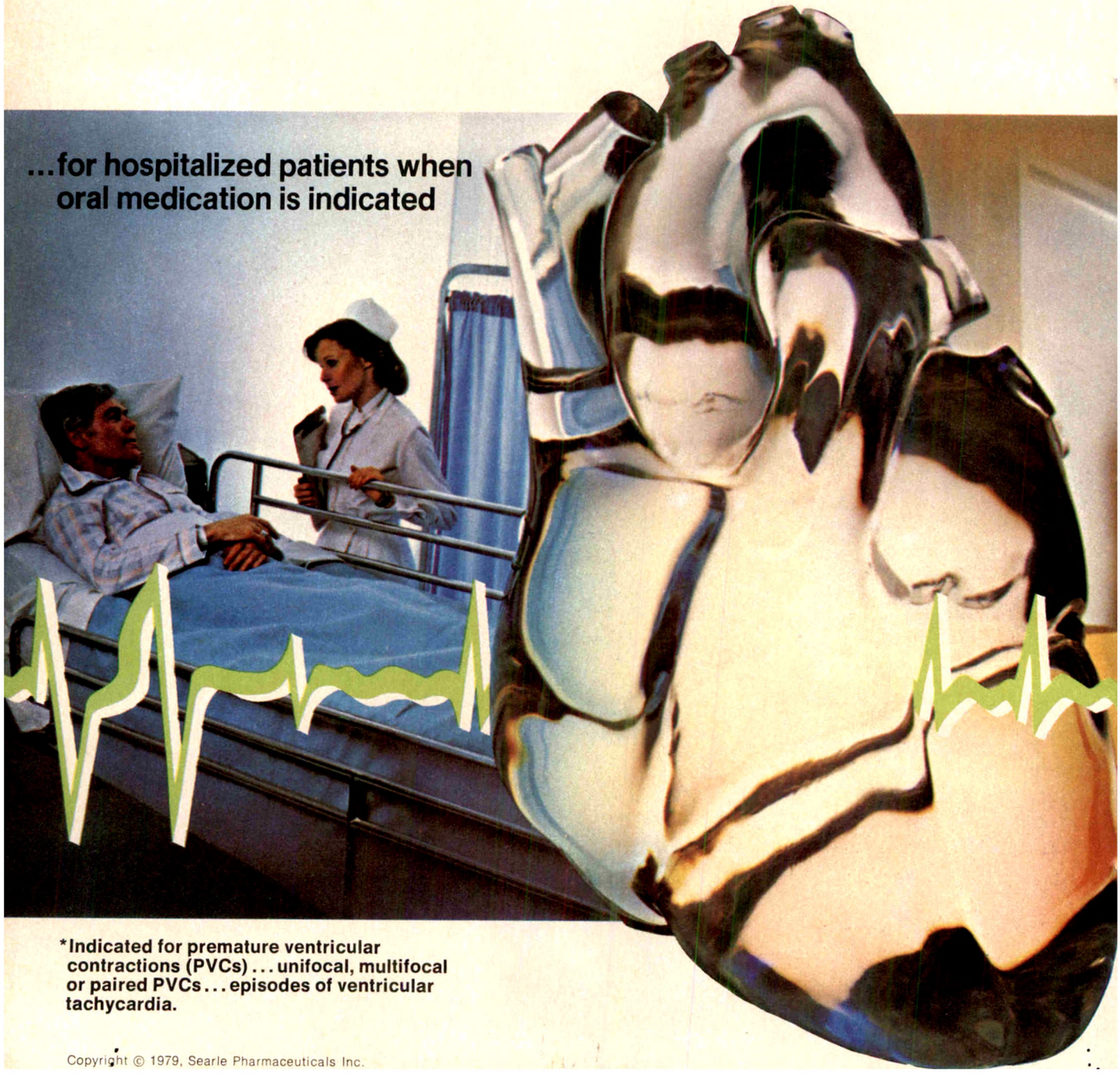
Making a long-term commitment to long-term recording.

For specific ventricular arrhythmias*

Norpace®

(disopyramide phosphate)

Right from the start



...for hospitalized patients when oral medication is indicated

*Indicated for premature ventricular contractions (PVCs)... unifocal, multifocal or paired PVCs... episodes of ventricular tachycardia.

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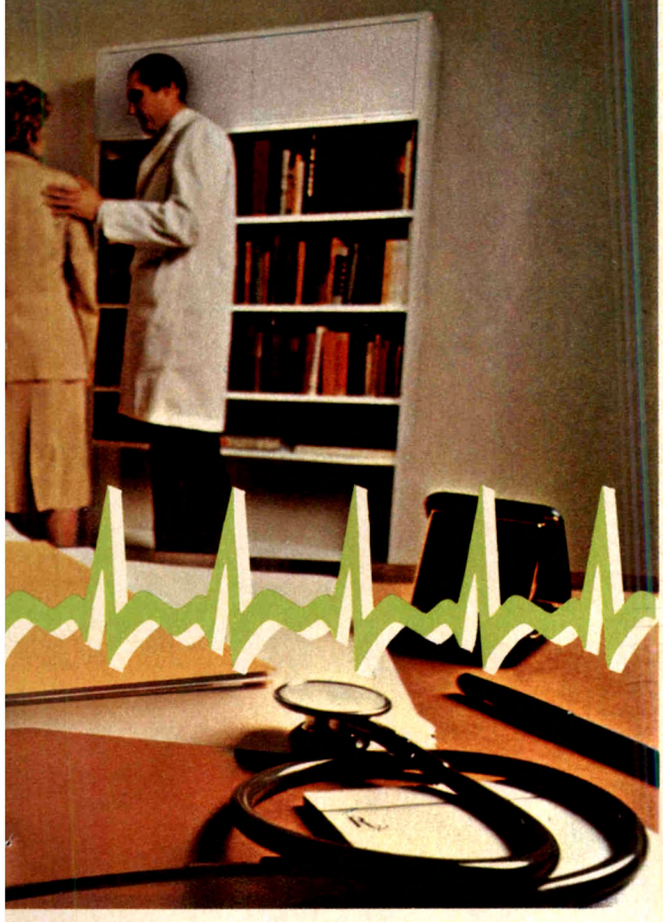
Particularly well suited to initial therapy

Demonstrated efficacy

Intensive clinical studies conducted prior to the release of Norpace (disopyramide phosphate) established its efficacy as an antiarrhythmic agent. And in the short time since its introduction, the drug has been employed in thousands of patients—most frequently initiated in the hospital, where the most challenging, critically ill patients are found. Norpace is now regularly prescribed by increasing numbers of cardiologists who have given it a rapidly expanding base in both hospital and outpatient use.

The efficacy of Norpace, proven in the clinical trials and confirmed in the more difficult hospitalized patients, qualifies it for initial therapy in newly diagnosed cases of ventricular arrhythmia. Such effectiveness was documented during a double-blind, multicenter clinical study involving five investigators.*

...as initial therapy in most outpatients



More favorable side-effects profile

When compared with quinidine sulfate, Norpace is notable for its lower incidence of severe side effects. These are mainly anticholinergic in nature, are usually mild and generally transient. If urinary hesitancy or other genitourinary side effects occur, they are often dose related and frequently may be managed by downward titration of the dose of Norpace. Urinary retention, however, may occasionally occur, particularly in the older patient. Males with benign prostatic hypertrophy are at particular risk.

The lupus-like syndrome often associated with procainamide therapy has not been seen with Norpace, even after several years of continuous Norpace therapy.

Lower dropout rate than quinidine

Efficacy of Norpace, coupled with its low incidence of severe side effects, can mean significantly fewer dropouts among your dysrhythmic patients. In a clinical study involving 62 patients in each treatment group, only 8.1% of patients discontinued Norpace therapy, as compared with 35.5% who discontinued quinidine.

High level of compliance

Even the best medication may not be taken as prescribed if it causes problems for the patient. With Norpace you are prescribing not only an effective medication, but you are prescribing one you can be reasonably confident the patient will take in accordance with your instructions.

Important considerations when prescribing Norpace (disopyramide phosphate)

Patients with compromised cardiac function due to any cause may experience either hypotension or a worsening of cardiac decompensation when taking drugs with negative inotropic effects, and the physician should be aware of this possibility with Norpace. Since Norpace is primarily excreted by the kidney, patients with renal impairment will require a reduced dosage due to prolongation of the effective half-life.

The dosage of Norpace should be individualized for each patient, and the Complete Prescribing Information consulted before prescribing. Special attention to the sections on *Clinical Pharmacology, Warnings,* and *Precautions* will be helpful in determining the proper dosage, particularly for the more complex patient.

Conclusion: Norpace represents a logical choice for both initial and maintenance therapy either in hospitalized patients or in outpatients.

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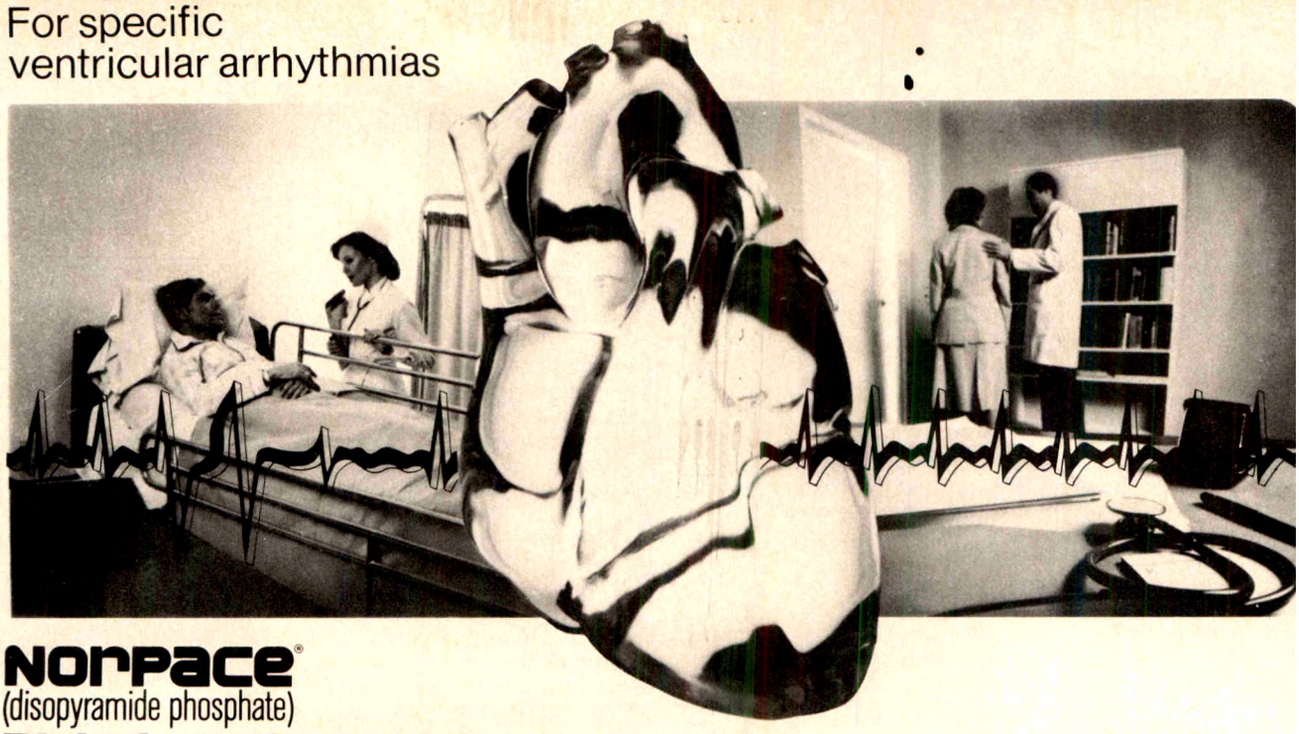
Please see the next page for a brief summary of prescribing information.

For specific ventricular arrhythmias



Norpace®
(disopyramide phosphate)

Right from the start

Before prescribing Norpace (disopyramide phosphate), please consult current complete prescribing information, a summary of which follows:

Indications: Norpace is indicated for suppression and prevention of recurrence of the following cardiac arrhythmias when they occur singly or in combination: unifocal premature (ectopic) ventricular contractions; premature (ectopic) ventricular contractions of multifocal origin; paired premature ventricular contractions (couplets); and episodes of ventricular tachycardia (persistent ventricular tachycardia is ordinarily treated with D.C. cardioversion).

Norpace is equally effective in treating the above arrhythmias in both digitalized and nondigitalized patients. It is also equally effective in treating primary cardiac arrhythmias and those which occur in association with organic heart disease including coronary artery disease. Oral Norpace has not been adequately studied in patients with acute myocardial infarction or in patients with persistent ventricular tachycardia or atrial arrhythmias and is not indicated for arrhythmias due to digitalis intoxication. The value of antiarrhythmic drugs in preventing sudden death in patients with serious ventricular ectopic activity has not been established.

Contraindications: Cardiogenic shock, preexisting second- or third-degree AV block (if no pacemaker is present), or known hypersensitivity to the drug.

Warnings: Severe hypotension has been observed primarily in patients with primary cardiomyopathy or inadequately compensated congestive heart failure. If hypotension develops Norpace should be discontinued promptly unless hypotension is due to the arrhythmia.

Norpace should not be used in the presence of poorly compensated or uncompensated congestive heart failure unless it is exacerbated by or caused by an arrhythmia and proper treatment including optimal digitalization has been accomplished. In patients with marginally compensated heart failure or with a history of heart failure, Norpace may worsen cardiac decompensation. In these patients, progressing congestive heart failure should generally be treated with cardiac glycosides and diuretics and the course of treatment closely followed. Norpace dosage should be reduced or discontinued if adequate control of congestive failure is not attained. Patients receiving concomitant therapy with more than one antiarrhythmic drug must be carefully monitored for serious negative inotropic effects or excessively prolonged conduction, evidenced by widening of the QRS complex and/or prolongation of the Q-T interval.

If first-degree heart block develops, the dosage of Norpace should be reduced. If the block persists, continuation of Norpace must depend upon an assessment of the benefit versus the risk. Development of second- or third-degree AV block or uni-, bi- or trifascicular block requires discontinuation of Norpace, unless the ventricular rate is adequately controlled by a pacemaker.

Because of its anticholinergic properties, Norpace should not be used in patients with glaucoma, myasthenia gravis or urinary retention, unless adequate overriding measures are taken.

Precautions: If significant widening (greater than 25%) of the QRS complex occurs, Norpace should be discontinued. If Q-T prolongation greater than 25% occurs and if ectopy continues, monitor closely and consider discontinuing Norpace.

Patients with atrial flutter or fibrillation should be digitalized prior to Norpace administration to ensure that drug-induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits.

The effect of Norpace is presently uncertain in patients with sick sinus syndrome, Wolff-Parkinson-White syndrome, or bundle branch block.

Patients with myocarditis or other cardiomyopathy may develop significant hypotension in response to the usual dosage of Norpace.

Norpace should be administered cautiously to patients who are receiving or who have recently received other antiarrhythmic drugs. Excessive widening of the QRS complex and/or prolongation of the Q-interval may occur in such instances.

Norpace dosage should be reduced in patients with impaired renal o hepatic function and the electrocardiogram carefully monitored for signs of overdosage.

Antiarrhythmic drugs may be ineffective in patients with hypokalemia Therefore, any potassium deficit should be corrected before instituting Norpace therapy.

Use in Pregnancy and Lactation: Safe use in pregnancy has not been established. Norpace has been reported to stimulate contractions of th pregnant uterus. The use of Norpace in pregnant women requires that the potential benefit be weighed against possible hazards to the fetus.

It is not known whether disopyramide is excreted in human milk. However, studies in rats have shown that the concentration of disopyramide and its metabolites is up to three times greater in milk than in plasma. If use of the drug is deemed essential, an alternate method of infant feeding should be instituted.

Labor and Delivery: The effects of Norpace on the fetus during delivery or on the course of labor and delivery are unknown.

Pediatrics: The safety and effectiveness of Norpace in children have not been established.

Adverse Reactions: *Anticholinergic:* dry mouth, urinary hesitancy, constipation, blurred vision, dry nose/eyes/throat, urinary retention. *Genitourinary:* urinary frequency and urgency. *Gastrointestinal:* nausea pain/bloating/gas, anorexia, diarrhea, vomiting. *General:* nervousness dizziness, general fatigue/muscle weakness, headache, malaise. *Cardiovascular:* hypotension, congestive heart failure, cardiac conduction disturbances, edema/weight gain, shortness of breath, syncope, chest pain. *Dermatologic:* generalized rash/dermatoses. The following have occurred, but a causal relationship is uncertain: impotence, depression, insomnia, dysuria, and hypoglycemia (usually i patients with impaired liver function). Acute psychosis, cholestatic jaundice, and agranulocytosis, all three reversible, have been reported.

Dosage and Administration: Dosage must be individualized for each patient on the basis of response and tolerance. The usual adult dosage is 400 to 800 mg per day given in divided doses four times daily. The recommended dosage schedule for most adults is 150 mg every six hours. For patients weighing less than 110 pounds (50 kg) the recommended dosage is 100 mg every six hours.

If rapid control of arrhythmia is essential, an initial loading dose of 300 mg of Norpace (200 mg for patients weighing less than 110 pounds) is recommended For patients with cardiomyopathy or possibl cardiac decompensation, a loading dose should not be given and the initial dose limited to 100 mg every six hours, with subsequent dosage adjustments made gradually under close monitoring.

See current complete prescribing information for dosage recommendations.

How Supplied: Capsules containing 100 mg or 150 mg of disopyramid base. Available in bottles of 100 and 500 capsules.

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represents the state-of-the-art in highly advanced high speed ultrasonic electronic scanners. A real time cross sectional, two-dimensional "B" mode image of the heart structure can be clearly obtained by positioning the probe on the chest wall. Valve movements, chamber size and detail of the internal structures of the heart can be clearly observed, measured and diagnosed. The SSH-10A is also capable of obtaining two "M" mode tracings simultaneously as well as Kymograph* studies. With its 78° true wide angle sector range, the SSH-10A provides a permanent EKG, phono-cardiogram, and patient ID with digital caliper read-out on the CRT in the "B"

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When it comes to providing a accurate picture of your patie heart condition, there are two things to remember, resolutio and Toshiba.

*Kymograph is a composite of "B" mode images obtained from a gated EKG.

Details about e heart you never thought possible

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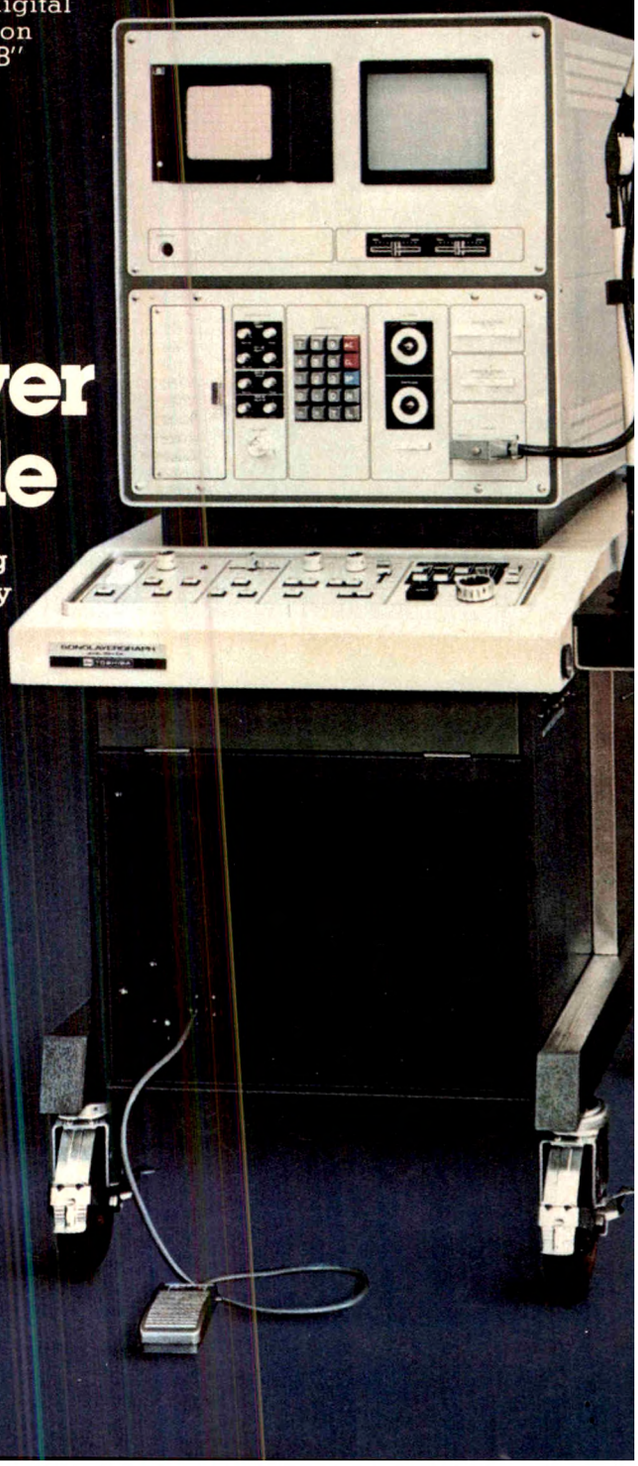

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The coronary

with significant hyperlipidemia and

Candidate for Atromid-S®

(clofibrate) Capsules 500 mg

ATROMID-S (clofibrate) is *not* for everyone with elevated lipids. It *is* for the patient with significant hyperlipidemia and a high risk of coronary artery disease. Because patient selection and the proper application of ancillary measures are so important to therapeutic success with ATROMID-S, the following steps should be taken before prescribing:

Important Note: This is not an innocuous drug. Strict attention should be paid to the Indications, Contraindications, and Warnings in prescribing information on back of the following page.

Ayerst®

Ayerst Laboratories
New York, N.Y. 10017

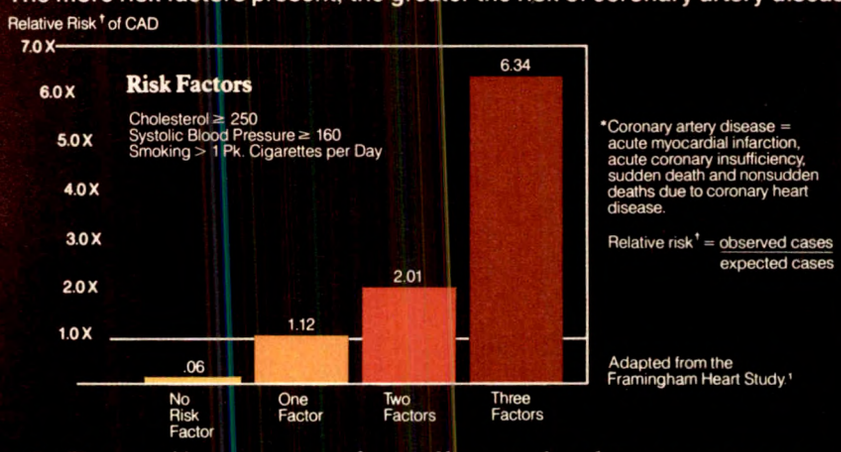
prone patient

high risk of coronary artery disease

1. Assess coronary risk

In addition to elevated lipid levels, consideration should be given to other factors that increase the risk of coronary artery disease (CAD): strong family history of CAD, low serum levels of high density lipoprotein, marked obesity, continued cigarette smoking, hypertension not satisfactorily controlled with medication. Drug therapy should be more strongly considered in younger patients. It should be noted, however, that correcting a given factor does not assure that risk will revert to what it would have been had that factor never been present.

The more risk factors present, the greater the risk of coronary artery disease



*Coronary artery disease = acute myocardial infarction, acute coronary insufficiency, sudden death and nonsudden deaths due to coronary heart disease.

Relative risk† = observed cases / expected cases

Adapted from the Framingham Heart Study.[1]

2. Prescribe appropriate diet and other measures

Treatment of primary hyperlipidemia should begin with a diet specific for the lipid abnormality involved. Diet, weight reduction, exercise, and good control of diabetes may be sufficient to correct the lipid problem.

3. But when diet and other measures are not enough and other drugs are inappropriate or inadequate, prescribe Atromid-S (clofibrate)

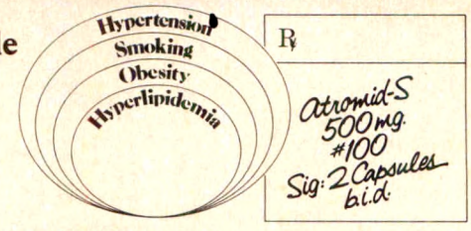
The most significant benefit can be expected in patients with more than one coronary risk factor who experience a significant reduction in cholesterol and/or triglyceride levels after an adequate trial of ATROMID-S. Diet and other appropriate measures must be continued for optimal lipid lowering. If the lipid response is not favorable, the drug should be discontinued.

As an adjunct to diet Atromid-S® (clofibrate) Capsules 500 mg
For the coronary-prone patient with significant hyperlipidemia

Reference: 1. The Framingham Heart Study: U.S. Department of Health, Education, and Welfare, Public Health Service,.

As an adjunct to diet and other appropriate measures Atromid-S® (clofibrate)

Helps correct the lipid factor in the high-risk profile



(For full product information, see package circular.)

ATROMID-S® Brand of Clofibrate

Antilipidemic agent for reduction of elevated serum lipids

ACTIONS: ATROMID-S is an antilipidemic agent. It acts to lower elevated serum lipids by reducing the very low density lipoprotein fraction (S_f20-400) rich in triglycerides. Serum cholesterol, especially the low density lipoprotein fraction (S_f0-20), is also decreased, particularly in those whose cholesterol levels are elevated at the outset.

The mechanism of action has not been established definitively. In man, clofibrate reduces cholesterol formation early in the biosynthetic chain. In addition, clofibrate has been shown to cause increased excretion of neutral sterols.

Animal studies suggest that clofibrate interrupts cholesterol biosynthesis prior to mevalonate formation.

INDICATIONS: This is not an innocuous drug. Strict attention should be paid to the Indications, Contraindications, and Warnings.

Treatment of primary hyperlipidemia should begin with a diet specific for the type of hyperlipidemia.[1] Diet, weight reduction, exercise, and good control of diabetes mellitus lead to improved lipid levels and may obviate the need for antilipidemic drugs.

ATROMID-S may be utilized as adjunctive therapy in patients with significant hyperlipidemia and a high risk of coronary artery disease who do not respond adequately to diet and weight loss. Before using ATROMID-S in a patient, consideration should be given to whether other antilipidemic drugs are more appropriate in view of the serious adverse findings with ATROMID-S reported in two large clinical trials (see WARNINGS). In addition, assessment of risk of coronary artery disease should include consideration of such factors, in addition to lipid levels, as strong family history of coronary heart disease, low serum levels of high density lipoprotein, marked obesity, continued smoking, use of oral contraception, and hypertension that is not satisfactorily controlled with medication. Drug therapy should be more strongly considered in younger patients and in those with a history of pancreatitis or abdominal pain associated with markedly elevated triglyceride levels.

ATROMID-S is a drug of first choice for primary dysbetalipoproteinemia (Type III hyperlipidemia), but in other types of hyperlipidemia certain other antilipidemic drugs may prove more effective in individual patients particularly where cholesterol is the lipid of greatest concern.

Clofibrate is not indicated for community-wide prevention of ischemic heart disease, but may be useful in patients individually selected for recognized disorders of fat metabolism which may predispose them to an increased risk of heart disease.

Response to ATROMID-S is variable, and it is not always possible to predict from the lipoprotein type or other factors which patients will obtain favorable results. It is essential that lipid levels be assessed and that the drug be discontinued in any patient in whom lipids are not effectively altered. ATROMID-S usually lowers elevated serum triglycerides to a greater extent than elevated serum cholesterol.

CONTRAINDICATIONS: Clofibrate is contraindicated in pregnant women. While teratogenic studies have not demonstrated any effect attributable to clofibrate, it is known that serum of the rabbit fetus accumulates a higher concentration of clofibrate than that found in maternal serum, and it is possible that the fetus may not have developed the enzyme system required for the excretion of clofibrate.

It is contraindicated in lactating women since it is not known if clofibrate is secreted in the milk.

It is contraindicated in patients with clinically significant hepatic or renal dysfunction.

It is contraindicated in patients with primary biliary cirrhosis since it may raise the already elevated cholesterol in these cases.

WARNINGS:

In a large prospective study involving 5,000 patients in a clofibrate-treated group and 5,000 in a placebo-treated group followed for an average of five years on drug or placebo and one year beyond (the WHO study), there was a statistically significant 36% higher mortality due to noncardiovascular causes in the clofibrate-treated group than in a comparable placebo group. Half of this difference was due to malignancy; other causes of death included postcholecystectomy complications and pancreatitis.[2] In another prospective study involving 1,000 clofibrate- and 3,000 placebo-treated patients followed for an average of six years on drug or placebo (the Coronary Drug Project study), the noncardiovascular mortality rate, including that of malignancy, was not significantly different in the clofibrate- and placebo-treated groups.[3] This should not be interpreted to mean that clofibrate is not associated with an increased risk of noncardiovascular death because the patients in the Coronary Drug Project were much older than those in the WHO study and they all had had a previous myocardial infarction so that the deaths in the Coronary Drug Project were overwhelmingly due to cardiovascular causes and it would have been very difficult to discern a clofibrate-associated risk of death due to noncardiovascular causes if it existed. Both studies demonstrated that clofibrate users have twice the risk of developing cholelithiasis and cholecystitis requiring surgery as do nonusers.

A potential benefit of clofibrate was, however, reported in the WHO study which involved patients with hypercholesterolemia and no history of myocardial infarction or angina pectoris. In this study, there was noted a statistically significant 25% decrease in subsequent nonfatal myocardial infarctions in the clofibrate-treated group when compared with the placebo group. There was no difference in incidence of fatal myocardial infarction in the two groups. If the study had been continued longer, had included diet, had been restricted to patients who had both hyperlipidemia and increased risk factors *and* who obtained significant clofibrate-induced reduction in serum lipids, it is possible that it may have shown a decrease in fatal myocardial infarctions. In the Coronary Drug Project study, which involved patients with or without hypercholesterolemia and/or hypertriglyceridemia and with a history of previous myocardial infarction, there was no significant difference in incidence of either nonfatal or fatal myocardial infarction between the clofibrate- and placebo-treated groups.[2]

As a result of these and other studies, the following can be stated:

1. Clofibrate, in general, causes a relatively modest reduction of serum cholesterol and a somewhat greater reduction of serum triglycerides. In Type III hyperlipidemia, however, substantial reductions of both cholesterol and triglycerides can occur with use of clofibrate.
2. No study to date has shown a convincing reduction in incidence of *fatal* myocardial infarction.
3. A significantly increased incidence of cholelithiasis has been demonstrated consistently in clofibrate-treated groups, and an increase in morbidity from this complication and mortality from cholecystectomy must be anticipated during clofibrate treatment.
4. Several types of other undesirable events have been associated in a statistically significant way with clofibrate administration in the WHO or the Coronary Drug Project studies. There was an increase in incidence of noncardiovascular deaths reported in the WHO study. There was an increase in cardiac arrhythmias and intermittent claudication and in definite or suspected thromboembolic events and angina reported in the Coronary Drug Project, which was not, however, reported in the WHO study.
5. Administration of clofibrate to mice and rats in long-term studies at eight times the human dose, and to rats at five times the human dose, resulted in a higher incidence of benign and malignant liver tumors than in controls. Lower doses were not included in these studies.

BECAUSE OF THE HEPATIC TUMORIGENICITY OF CLOFIBRATE IN RODENTS AND THE POSSIBLE INCREASED RISK OF MALIGNANCY ASSOCIATED WITH CLOFIBRATE IN THE HUMAN, AS WELL AS THE INCREASED RISK OF CHOLELITHIASIS, AND BECAUSE THERE IS NOT, TO DATE, SUBSTANTIAL EVIDENCE OF A BENEFICIAL EFFECT ON CARDIOVASCULAR MORTALITY FROM CLOFIBRATE, THIS DRUG SHOULD BE UTILIZED ONLY FOR THOSE PATIENTS DESCRIBED IN THE INDICATIONS SECTION, AND SHOULD BE DISCONTINUED IF SIGNIFICANT LIPID RESPONSE IS NOT OBTAINED.

Concomitant Anticoagulants

CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCT WITH ATROMID-S. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED USUA BY ONE-HALF (DEPENDING ON THE INDIVIDUAL CASE) TO MAINTAIN THE PROTHRON TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT P THROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DET MINED THAT THE PROTHROMBIN LEVEL HAS BEEN STABILIZED.

Avoidance of Pregnancy

Strict birth control procedures must be exercised by women of childbearing potential. In pati who plan to become pregnant, clofibrate should be withdrawn several months before conc tion. Because of the possibility of pregnancy occurring despite birth control precaution patients taking clofibrate, the possible benefits of the drug to the patient must be weighed aga possible hazards to the fetus.

PRECAUTIONS: Before instituting therapy with clofibrate, attempts should be made to cor serum lipids with appropriate dietary regimens, weight loss in obese patients, control of diab mellitus, etc.

Because of the long-term administration of a drug of this nature, adequate baseline stu should be performed to determine that the patient has significantly elevated serum lipid lev Frequent determinations of serum lipids should be obtained during the first few month ATROMID-S administration, and periodic determinations thereafter. The drug should be v drawn after three months if response is inadequate. However, in the case of xanth tuberosum, the drug should be employed for longer periods (even up to one year) provided there is a reduction in the size and/or number of the xanthomata.

Subsequent serum lipid determinations should be done to detect a paradoxical rise in se cholesterol or triglyceride levels. Clofibrate will not alter the seasonal variations of serum cho terol peak elevations in midwinter and late summer and decreases in fall and spring. If the dru discontinued, the patient should be continued on an appropriate hypolipidemic diet, and serum lipids should be monitored until stabilized, as a rise in these values to or above the orig baseline may occur.

During clofibrate therapy, frequent serum transaminase determinations and other liver func tests should be performed since the drug may produce abnormalities in these parameters. Th effects are usually reversible when the drug is discontinued. Hepatic biopsies are usually w normal limits. If the hepatic function tests steadily rise or show excessive abnormalities, the d should be withdrawn. Therefore use with caution in those patients with a past history of jaun or hepatic disease.

Since cholelithiasis is a possible side effect of clofibrate therapy, appropriate diagnostic pr dures should be performed if signs and symptoms related to disease of the biliary system sh occur.

Clofibrate may produce "flu like" symptoms (muscular aching, soreness, cramping). The ph cian should differentiate this from actual viral and/or bacterial disease.

Use with caution in patients with peptic ulcer since reactivation has been reported. Whether th drug-related is unknown.

Complete blood counts should be done periodically since anemia, and more freque leukopenia have been reported in patients who have been taking clofibrate.

Various cardiac arrhythmias have been reported with the use of clofibrate.

Several investigators have observed in their studies that clofibrate may produce a decreas cholesterol linoleate but an increase in palmitoleate and oleate, the latter being consid atherogenic in experimental animals. The significance of this finding is unknown at this ti

ADVERSE REACTIONS: Of the pertinent reactions, the most common is nausea. Less freque encountered gastrointestinal reactions are vomiting, loose stools, dyspepsia, flatulence, abdominal distress. Reactions reported less often than gastrointestinal ones are headac dizziness, and fatigue; muscle cramping, aching, and weakness; skin rash, urticaria, pruritus; dry brittle hair, and alopecia.

The following reported adverse reactions are listed alphabetically by systems:

Cardiovascular: increased or decreased angina; cardiac arrhythmias; both swelling phlebitis at site of xanthomas

Dermatologic: skin rash; alopecia; allergic reaction including urticaria; dry skin and dry br hair; pruritus

Gastrointestinal: nausea; diarrhea; gastrointestinal upset (bloating, flatulence, abdominal tress); hepatomegaly (not associated with hepatotoxicity); gallstones; vomiting; stomatitis gastritis

Genitourinary: impotence and decreased libido. Findings consistent with renal dysfunctior evidenced by dysuria, hematuria, proteinuria, decreased urine output. One patient's renal bio suggested "allergic reaction."

Hematologic: leukopenia; potentiation of anticoagulant effect; anemia; eosinophilia

Musculoskeletal: myalgia (muscle cramping, aching, weakness); "flu like" symptoms; arthra

Neurologic: fatigue, weakness, drowsiness; dizziness; headache

Miscellaneous: weight gain; polyphagia

Laboratory Findings: abnormal liver function tests as evidenced by increased transamin (SGOT and SGPT), BSP retention, and increased thymol turbidity; proteinuria; increased crea phosphokinase

Reported adverse reactions whose direct relationship with the drug has not been establish peptic ulcer, gastrointestinal hemorrhage, rheumatoid arthritis, tremors, increased perspirat systemic lupus erythematosus, blurred vision, gynecomastia, thrombocytopenic purpura.

DOSAGE AND ADMINISTRATION: *Initial:* The recommended dosage for adults is 2 g dai divided doses. Some patients may respond to a lower dosage.

Maintenance: Same as for initial dosage.

Note: In children, insufficient studies have been done to show safety and efficacy.

DRUG INTERACTIONS: Caution should be exercised when anticoagulants are given in conju tion with ATROMID-S. The dosage of the anticoagulant should be reduced usually by one- (depending on the individual case) to maintain the prothrombin time at the desired leve prevent bleeding complications. Frequent prothrombin determinations are advisable until it been definitely determined that the prothrombin level has been stabilized.

MANAGEMENT OF OVERDOSAGE: While there has been no reported case of overdos should it occur, symptomatic supportive measures should be taken.

HOW SUPPLIED: No. 243—ATROMID-S—Each capsule contains 500 mg clofibrate, in bottle 100.

REFERENCES: 1. Coronary Risk Handbook (1973), American Heart Association. **2.** Report f the Committee of Principal Investigators: A cooperative trial in the primary prevention of isch mic heart disease using clofibrate, Br. Heart J. *40*:1069, 1978. **3.** The Coronary Drug Pro Research Group: Clofibrate and niacin in coronary heart disease, J.A.M.A. *231*:360, 1975

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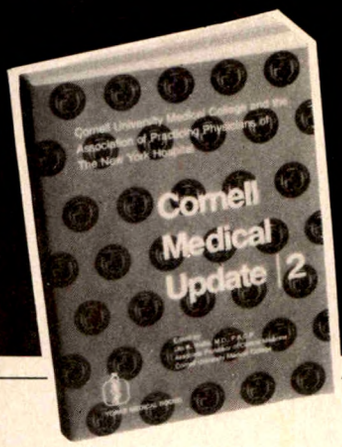

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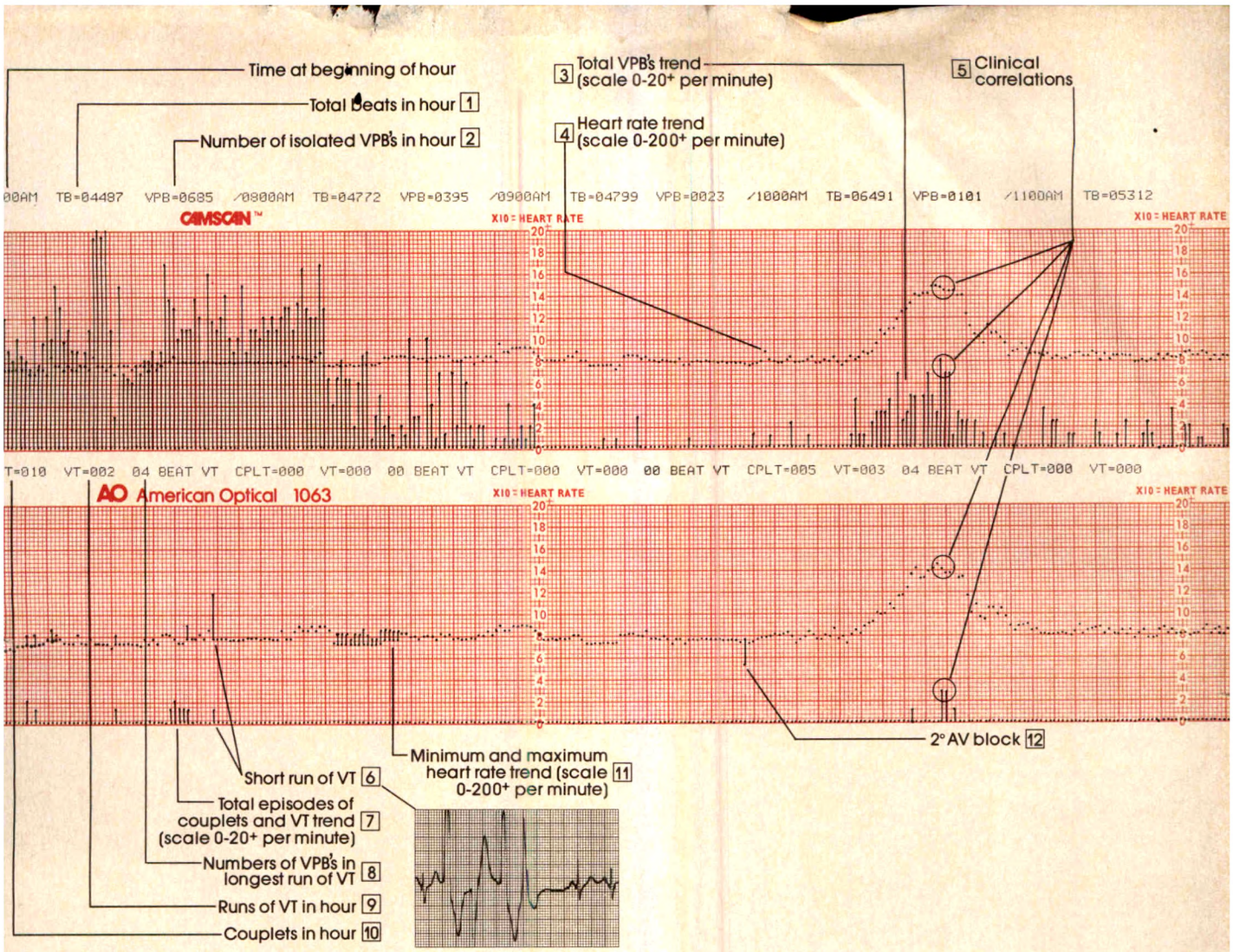

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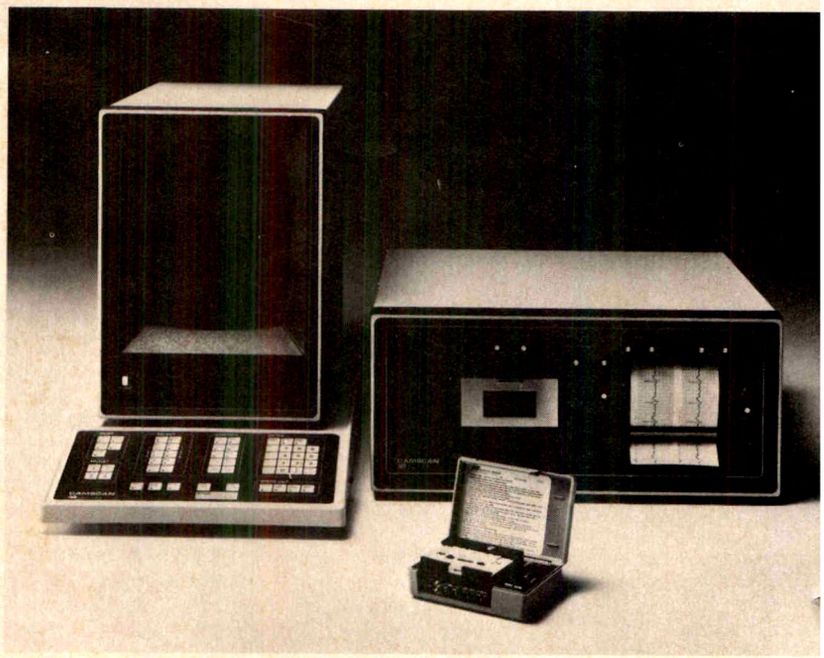

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Structural Changes in a Porcine Xenograft After Implantation for 105 Months

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Morphologic studies including light microscopy and transmission and scanning electron microscopy were performed on a formaldehyde-fixed porcine xenograft prosthesis that functioned well for 8 years and had been implanted for 105 months in the tricuspid valve position. It is the oldest implanted valve studied in this manner. Although all leaflets had some gross deterioration, only one had adherent thrombus. The degenerative changes in the connective tissue from all leaflets were similar to those recently reported in glutaraldehyde-fixed porcine valves implanted for shorter periods. The surfaces of the two nonthrombosed leaflets and small portions of the surface of the thrombosed leaflet were endothelized, and the endothelium appeared to have little or no effect on the degenerative changes in the subjacent connective tissue. Further, the endothelium did not extend over the examined portion of the synthetic anulus of the prosthesis, suggesting that its origin was possibly from cells circulating in the blood.

The glutaraldehyde-fixed porcine xenograft valve has several advantages over other prostheses used for replacement of human cardiac valves. These include central flow with hemodynamics nearly the same as those of the natural valve,[1,2] a greatly decreased incidence of thrombosis and embolism,[3] and a durability considerably greater than that of previous types of tissue valves. The durability of porcine xenografts will probably be less than that of mechanical prostheses, but the rate of failure has not yet reached a sufficient level to permit firm predictions of expected life.[3] Electron microscopic examination of removed valves may help in predicting durability.

The light and electron microscopic findings in glutaraldehyde-fixed porcine xenografts implanted for as long as 76 months have recently been published.[4–6] We have examined a formaldehyde-fixed porcine xenograft implanted for 105 months, and report our findings because this is the oldest reported implanted xenograft studied with light, scanning and transmission electron microscopy and because of the unexpected durability of a formalin-fixed xenograft valve.

Case Report

The Hancock (Hancock Laboratories, Anaheim, California) porcine xenograft we studied was fixed and stored in 10 percent acetate-buffered formalin on May 9, 1969 and was mounted on August 14, 1969. On October 28, 1969 it was implanted in the tricuspid position in an 18 year old woman found to have Ebstein's anomaly at 10 years. A patent foramen ovale was closed at the time of valve replacement. The patient was well until age 26 years, when cyanosis reappeared with dyspnea on exertion. Cardiac catheterization 1 year later showed tricuspid regurgitation, bidirectional shunting through a persistent patent foramen ovale and normal right atrial (mean 4 mm Hg) and right ventricular (21/5 mm Hg) pressures. On July 26, 1978 the tricuspid xenograft valve was removed and replaced with a glutaraldehyde-fixed porcine xenograft and the

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patent foramen ovale was closed with a Dacron® patch. Since then, the patient has been well and has normal exercise tolerance and no cyanosis.

Examination of the Removed Valve

All three leaflets of the removed valve were abnormal (Fig. 1). Two had smooth surfaces but were thickened and retracted toward the valve anulus. The third leaflet was covered on both its inflow and outflow surfaces with a layer of soft nodular material that appeared to be thrombus. Portions of each of the three leaflets were removed for light microscopy, transmission electron microscopy and scanning electron microscopy.

Hancock Laboratories kindly supplied us with an unimplanted formaldehyde-fixed porcine valve for analysis, but the tissue unfortunately had suffered from evaporation of the formaldehyde fluid during the 10 year interim, rendering it unsuitable as a control valve for critical comparison with the implanted specimen. To present some visual reference as a basis for perceiving changes occurring in the implanted valve, we removed appropriate specimens from an unused glutaraldehyde-fixed porcine prosthesis (Carpentier-Edwards, Edwards Laboratories, Santa Ana, California) and prepared them in the same manner as the specimens from the implanted valve removed at operation. These specimens had morphologic characteristics typical for aldehyde fixation, and were similar in all respects to those shown in control micrographs of glutaraldehyde-fixed valves described by Ferrans et al.[4] The electron micrographs (Figs. 2A, 3A and 4, A and B) are included for comparison with the surgical specimens.

Light microscopy: All specimens were fixed immediately in formalin and embedded in paraffin, and sections were stained with the hematoxylin-eosin, Masson, Verhoeff-Van Giessen and Alcian blue–periodic acid-Schiff methods.

Transmission electron microscopy: Portions of each leaflet were fixed in 4 percent phosphate-buffered glutaraldehyde, postfixed with 1 percent buffered osmic acid and embedded in Epon 812. One micron sections were stained with toluidine blue for light microscopic study. Ultrathin sections for electron microscopy were treated with uranyl acetate and lead citrate to enhance contrast.

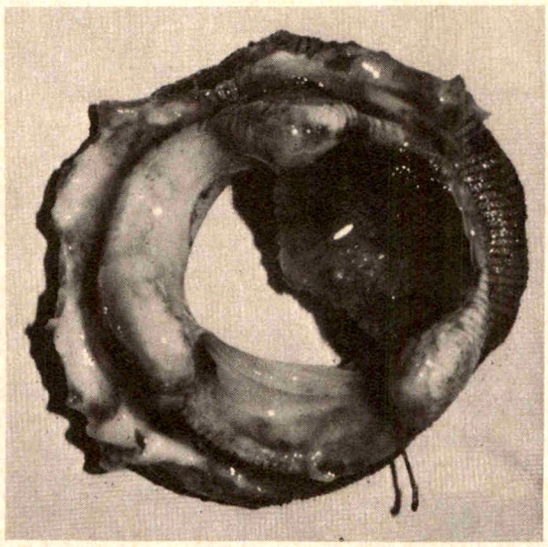

FIGURE 1. View of outflow aspect of explanted valve prosthesis. Two of the leaflets are retracted and reduced in substance; the third is covered with thrombus.

Scanning electron microscopy: Adjacent leaflet slices were fixed in 4 percent phosphate-buffered glutaraldehyde for 1 hour and postfixed in aqueous osmic acid for an additional hour. The tissues were subsequently rinsed in distilled water and dehydrated through graded ethanols to absolute ethanol and gradually displaced by 100 percent Freon®-113 over a period of 3 hours. They were then processed in a Parr Critical Point Dryer using Freon-13. The dried specimens were further divided for superior-inferior orientation and attached to aluminum stubs with silver paste, vacuum-evaporated, coated with gold-palladium and examined with an Hitachi SSM-2A scanning electron microscope.

Results

Light microscopy: The two retracted leaflets were covered on both surfaces by an endothelial cell layer separated from the underlying stroma by a subjacent pale band, and in places by a second discontinuous cell layer. The connective tissue substructure was acellular, hazy in appearance and had poorly defined lamination and surface condensations. The trichrome stain defined the collagen more clearly but the sections contained no elastic fibers after appropriate staining. The Alcian blue–periodic acid-Schiff reaction disclosed the loss of acid mucopolysaccharide ground substance present in unimplanted valve. However, it demonstrated the presence of acid mucopolysaccharide in the pale stratum beneath the endothelial cells.

The third leaflet was covered on both surfaces by thrombotic material consisting of variable proportions of fibrin matrix, red and white blood cells and macrophages. This material was tightly adherent to the underlying acellular connective tissue, but some channels or clefts containing fresh blood elements were present. Endothelium was present for short distances on the inflow surface where the fibrin layer was thin. It was separated from the underlying fibrin by a pale band of mucopolysaccharide-rich substance like that present in the other two leaflets. Connective tissue and histochemical stains disclosed appearances essentially similar to those observed in the retracted leaflets.

The 1 micron thick plastic (Epon®) sections of the control and damaged leaflets displayed in finer detail the morphologic features observed in the paraffin-embedded sections, but divulged no additional information.

Transmission electron microscopy: The principal changes in the two retracted leaflets from the implanted valve included endothelization of both surfaces, profound degeneration of the connective tissue and loss of fibroblasts. The endothelial cells were commonly attenuated, and were connected to one another by typical junctional complexes (Fig. 2B). They rested on a broad layer of loose, finely fibrillar matrix resembling a stratified endothelial basal laminar substance. In some places, a stratum of histiocytes was interposed between this delicate interstitium and the dense underlying connective tissue. The surfaces of the third leaflet were covered with an admixture of intact and degenerating fibrin, red and white blood cells, platelets and macrophages (Fig. 2, C and D). The stroma of all leaflets was composed of amorphous clumps, particles and remnants of collagen fibers of which only a few still retained a recognizable banding pattern (Fig. 3B). Although scattered small round electron-lucent areas, possibly representing lipid droplets, were seen in the stroma of the implanted valve, no intact cells were present.

Scanning electron microscopy: The surfaces of the retracted leaflets were covered with a continuous sheet of squamous cells arranged in a mosaic pattern (Fig. 4, C and D). Their close intercellular apposition could be appreciated in some areas, and short microvilli covered much of the cells'

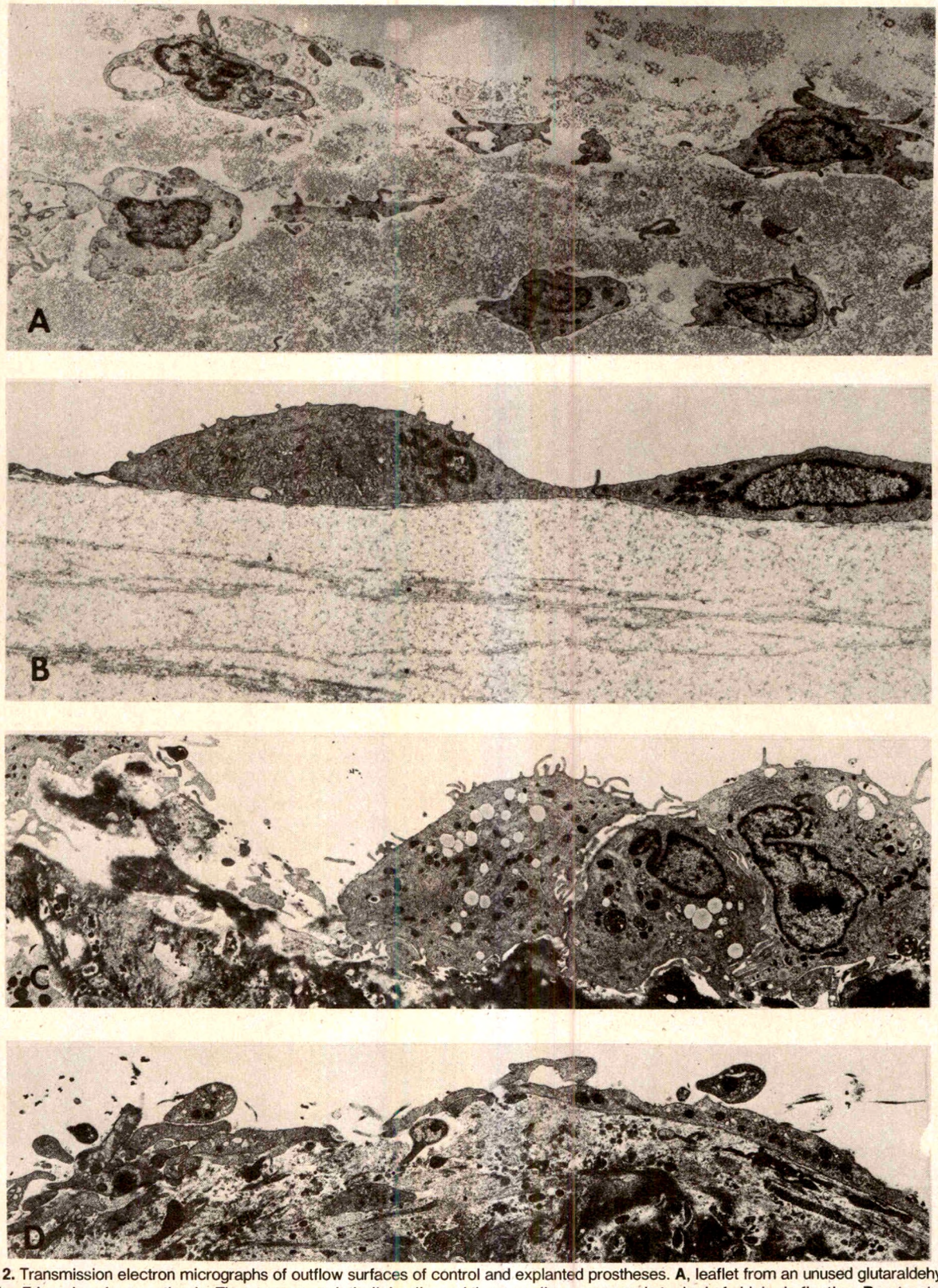

FIGURE 2. Transmission electron micrographs of outflow surfaces of control and explanted prostheses. **A**, leaflet from an unused glutaraldehyde-fixed Carpentier-Edwards valve prosthesis. There are no endothelial cells, and the overall appearance is typical of aldehyde fixation. **B**, retracted leaflet from explanted prosthesis. Typical endothelial cells form a continuous layer, resting on a stratum of loose, granular and fibrillar stroma. **C**, thrombosed leaflet from explanted prosthesis. The thrombotic material is partly covered by macrophages. **D**, adjacent area of leaflet pictured in Figure 2C. Platelets cover thrombotic material.

surface. The surfaces of the thrombosed leaflet were markedly irregular and coarse (Fig. 4E). Red blood cells could be identified, and other structures often suggested isolated cells of undetermined nature.

The surface of the fabric covering the anulus was composed of interlacing bundles of smooth fibers with scattered patches of fibrin, debris and a few red blood cells on its surface or entrapped in their interstices (Fig. 4F). Intact cells were not present.

Discussion

Fate of formaldehyde-fixed heterograft valves: The potential advantages of tissue valve prostheses led to extensive evaluation of formaldehyde-fixed heterograft valves during the late 1960's.[7,8] Clinical trials were abandoned when the rate of failure of these valves was found to be very high within only a few months after implantation.[9,10] Relatively early failure of these grafts was attributed to profound structural deterioration, resulting in severe stretching[11] or tearing[12] of the valve cups.

Pathologic changes within a few months of operation were of three types: (1) reaction to a foreign body at the graft-host interface; (2) a cell immunologic reaction seen over large areas of the valve tissue or focally on their surfaces; and (3) denaturation of collagen and elastin without cell infiltration, in the form of hyalinization, necrosis and disintegration of elastic fibers.[13] Light microscopy[11,12,14–16] revealed inflammatory cell infiltration at the base of cusps, focal histiocytic invasion of the valve substance, calcification and acellular homogeneous appearing collagen with only focal areas of fibrillary appearance. The leaflet surfaces were sometimes covered by thrombus, and often complete necrosis with disruption of valve substance was seen.

Few electron micrographs of implanted formaldehyde-fixed valves have been published. One such micrograph[12] revealed a few collagen fibrils and apparent active phagocytosis by a macrophage of collagen and elastin. Electron micrographs[14] comparing glutaraldehyde-fixed and formaldehyde-fixed xenografts 8 months after implantation demonstrated denaturation and disappearance of collagen fibers in the formaldehyde-fixed valve, but better preservation of the ultrastructure of collagen fibers in the glutaraldehyde-fixed valve. An electron micrograph of a formaldehyde-fixed valve implanted for 3 months showed severe collagen degeneration with finely granular material similar to that in the valve in our study.[11] In the same study, the collagen in a second valve implanted for 14 months was said to be as well preserved by electron microscopy as that of unimplanted control valves.

The formaldehyde-fixed valve in our patient showed no evidence of failure clinically until 8 years after implantation. It also had significantly better preservation of collagen than published examples of failed formaldehyde-fixed valves; in fact, its ultrastructure was similar to that of published examples of glutaraldehyde-fixed valves of shorter implantation time.[5,6] It is known that the formaldehyde linkage with collagen is reversible,[13] and this had been cited as the reason for more rapid deterioration of valves tanned with formaldehyde than those tanned with glutaraldehyde. We have no explanation for the relatively good preservation of the ultrastructure of our valve.

Endothelization of the valve: The endothelization of two cusps of our valve is of some interest. We believe that the endothelium we observed on light and electron microscopy was of host (human) origin for two reasons: First, our own observations with scanning and transmission electron microscopy of unimplanted glutaraldehyde-fixed valves agree with the finding of Ferrans et al.[4] that endothelial cells are absent on the inflow and outflow surfaces before implantation. Because the endothelial layer is lost during processing, and because the processing of formaldehyde-fixed valves was similar to that used for glutaraldehyde-fixed valves, it is likely that formaldehyde-fixed valves similarly had no endothelial covering immediately before implantation. Second, other donor cell nuclei, such as the fibroblasts present in the stroma of unimplanted xenograft valves, had

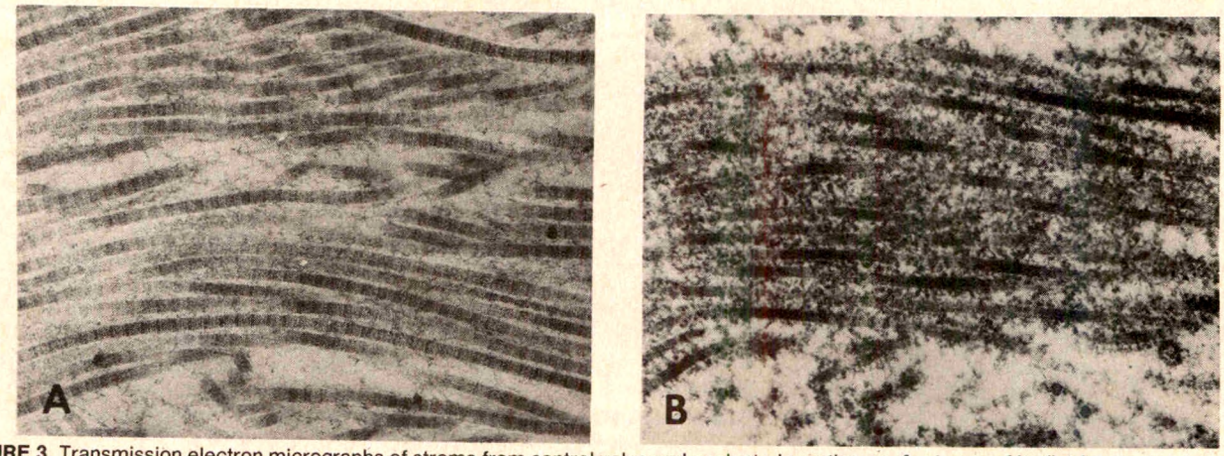

FIGURE 3. Transmission electron micrographs of stroma from control valve and explanted prostheses. **A**, stroma of leaflet from unimplanted Carpentier-Edwards prosthesis. Note the distinct banding and integrity of collagen fibrils. **B**, leaflet from the valve implanted for 105 months. The collagen fibrils are badly deteriorated, and typical banding is barely evident in a few fibrils.

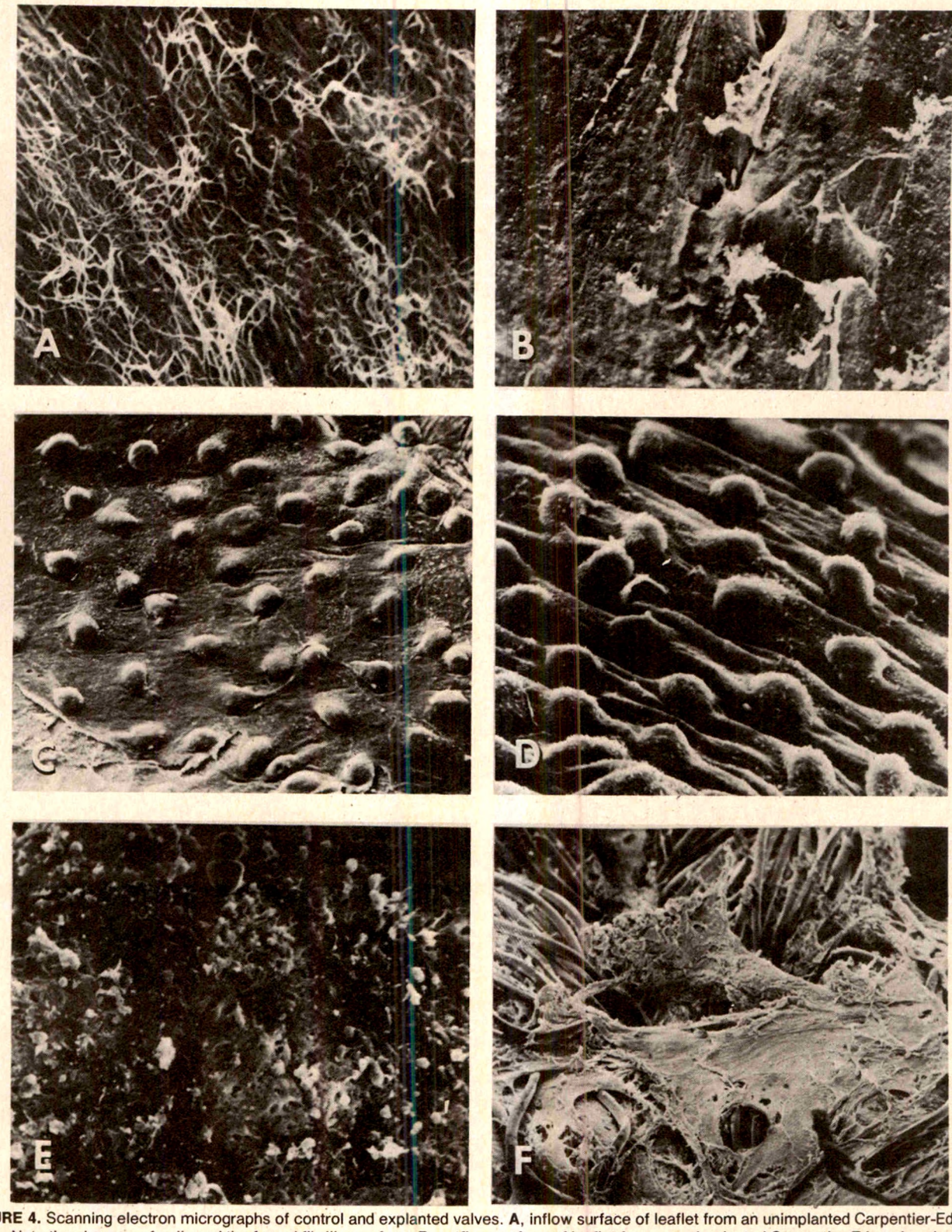

FIGURE 4. Scanning electron micrographs of control and explanted valves. **A**, inflow surface of leaflet from an unimplanted Carpentier-Edwards valve. Note the absence of cells and the frayed fibrillar surface. **B**, outflow surface of leaflet from an unimplanted Carpentier-Edwards valve. Note the absence of cells and the relatively smooth surface. **C**, surface of a retracted leaflet from the explanted valve. A continuous sheet of flattened endothelial cells arranged in a mosaic pattern covers the surface. **D**, endothelial cell surface at higher magnification. Fine microvilli cover surface of the cells. **E**, thromobotic leaflet. Note the absence of intact cells covering the coarse fibrin and debris. **F**, fabric sleeve covering the anulus. The synthetic fibers are partly covered with fibrin and ill-defined debris.

completely disappeared from this graft. Therefore, the healthy-appearing endothelium we observed probably arose from host cells.

We further postulate that the endothelial cells covering the leaflets probably originated from elements circulating in the blood rather than by spread from contiguous host vascular tissue because no endothelium could be seen on scanning electron microscopy on the surface of the stent, which completely separates the porcine tissue from host tissue.

We have found no published statements regarding endothelium covering formaldehyde-fixed leaflets after implantation. In published morphologic studies of glutaraldehyde-fixed porcine xenografts, endothelium has been seen covering leaflets by at least two[4,17] and perhaps a third[16] investigator, but only on valves implanted in the tricuspid position. Extensive endothelization has not been reported in a valve recovered from the left side of the heart. We propose that the extensiveness of endothelization of the valve we studied and in those instances cited earlier may have been related to lower shearing forces in the low pressure tricuspid position.

Structural changes in the valve: The histologic, histochemical and fine-structural appearance of the connective tissue stroma was similar in all leaflets of our valve implanted for 105 months, regardless of differences in surface structure. Structural changes were similar to those described by Ferrans et al.[4] in their glutaraldehyde-fixed specimens that had been implanted for the longest periods. The data from the studies of Ferrans,[4] Ashraf and Bloor[5] and their coworkers indicate that severe degeneration of collagen usually occurs within 12 months of implantation. The deterioration of collagen in our valve implanted for nearly 9 years was also severe, but it appeared no worse than that in their valves after 21 or more months of implantation. In both glutaraldehyde- and formaldehyde-fixed valves the structural degenerative changes and loss of porcine fibroblasts probably occurs relatively early, and subsequent functional failure may evolve over an extended period.

Factors affecting valve durability: Ferrans' group[4] suggested that collagen breakdown may be accelerated by hemodynamic forces. The unusual preservation of our formaldehyde-fixed valve may have been due in part to its position in the low pressure side of the heart rather than in the aortic or mitral site. Neither endothelization nor thrombotic vegetation on the surface of the formaldehyde-fixed tissue seemed to retard or accelerate collagen deterioration because the three leaflets had similar ultrastructural features. However, the thrombotic leaflet was more functionally intact and less retracted than the two endothelized cusps, suggesting that endothelization may predispose to tissue atrophy or retraction. Durability of glutaraldehyde-fixed prostheses in the right side of the heart may differ from durability in the left side of the heart because of two opposing factors: Stronger hemodynamic forces, by accelerating collagen deterioration, may lead to earlier prosthetic failure in the left side of the heart, whereas endothelization, by accelerating tissue contraction, may lead to earlier prosthetic failure in the right side. Long-term follow-up and critical anatomic evaluation of these prostheses may clarify the importance of factors affecting durability.

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Bilateral Cardiac Myxomas and Peripheral Myxomas in a Patient With Recent Myocardial Infarction

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Coronary arteriography, performed for recent anterior wall myocardial infarction in a 29 year old man, showed multiple aneurysms of the distal branches of the left coronary artery without evidence of obstructions in the major branches, and two clusters of abnormal vessels, supplying tumors in the right ventricle and the left atrium. At operation and histologic examination both tumors appeared to be myxomas. In addition, two myxomas, located elsewhere in the body, could be proven histologically.

Accounting for more than half of all cases, myxoma is the most frequent primary cardiac tumor. About 75 percent of myxomas originate in the left atrium; they are located less frequently in the right atrium, and rarely in the ventricles.[1–15] Ten cases of bilateral myxomas have been reported.[16,17]

Clinical manifestations of myxoma cordis encompass a variety of symptoms, resulting from valve obstruction, embolization and systemic illness. With current techniques it is nearly always possible to establish the diagnosis. However, because of unusual symptoms, the possibility of myxoma is occasionally overlooked. Recently we encountered a patient who presented with myocardial infarction and bilateral cardiac myxomas in combination with two myxomas located elsewhere in the body.

Case Report

A 29 year old man was referred to our department for coronary arteriography after a myocardial infarction sustained 3 months previously.

Past medical history: Parinaud syndrome (paralysis of upward gaze with abolition of movements of convergence and pupillary light reflexes) was noted in 1974. In the same year a myxoma of the subcutis of the right shoulder was excised. In 1975 a Hürthle cell adenoma of the thyroid gland was removed. Between 1974 and 1978 the patient had intermittent pains in both legs accompanied by tender red spots on the legs. He had been free of cardiac symptoms until his acute myocardial infarction.

Clinical features: At the time of admission to our department, several months after the myocardial infarction, the patient had no angina pectoris. On physical examination, blood pressure was 130/80 mm Hg. Heart sounds were normal and there were no heart murmurs and no bruits over the peripheral arteries. On the inner surface of the left thigh there was a pedunculated tumor. Some hyperreflexia of the right side of the body was noted.

The electrocardiogram showed inferior, anterior and lateral wall infarction with S-T segment elevations in the precordial leads. A chest X-ray film showed a slightly enlarged cardiac silhouette. The pulmonary vasculature was normal.

Laboratory examinations showed normal values for erythrocyte sedimentation rate, blood urea nitrogen, serum creatinine, hemoglobin, transaminases and serum proteins.

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Coronary arteriography and left ventricular angiography: An abnormal large atrial branch of the left circumflex artery divided into a cluster of small vessels (Fig. 1). Flow of contrast medium from the cluster to the left atrial cavity was observed. A branch of the proximal right coronary artery coursing to the same left atrial area showed similar characteristics. Two branches of the right coronary artery terminated as clusters of small vessels in the region of the right ventricle (Fig. 2, top). The terminal branches of the left anterior descending and circumflex arteries showed distally longitudinal narrowings, continuing as aneurysmal dilatations (Fig. 2, bottom). Apart from these changes the coronary arteries were normal.

Left ventricular angiography revealed akinesia of the apex and a large portion of the anterior wall. Because the angiographic pattern suggested intracardiac tumor growth, we performed echocardiography and supplementary angiographic studies.

Echocardiography: A mass in the left atrium appeared, in diastole, as multiple abnormal echoes behind the anterior mitral valve leaflet. A second mass, located in the right ventricle, moved into the right ventricular outflow tract in systole.

Angiography of the left atrium showed a filling defect caused by a large lobulated tumor. Right atrial injections revealed a round smooth-walled mobile tumor in the right ventricular outflow tract. Pressure recordings showed no gradients across the mitral valve and the right ventricular outflow tract.

Scintigraphy of the lungs with technetium-99m revealed no abnormalities. Reviewing the *carotid angiogram* of 1974 we could detect no obstructions or aneurysms of the cerebral vessels.

Surgical findings: The left ventricle was moderately enlarged. Fibrous scar tissue extended from the apex to anterior and lateral walls. With use of extracorporeal circulation the heart was entered through both the left and the right atria. In the right ventricular outflow tract there was a grey-red glistening tumor attached to the anterior wall by a small pedicle. Extirpation of the tumor necessitated incision through the entire ventricular wall. Two large arteries supplying the tumor were ligated. The left atrial tumor was more friable and was attached over a large area to the interatrial septum. A portion of the atrial septum was excised to remove this tumor. The defect was closed with a Teflon® patch.

Pathologic findings: The tumors of the right ventricle (Fig. 3, top) and left atrium (Fig. 3, bottom) measured 48 by 50 by 28 mm and 42 by 27 by 24 mm, respectively. The surface of the first tumor was smooth, in contrast to that of the second one, which was irregular and partly villous. Both tumors showed the characteristic histologic findings of myxoma (Fig.

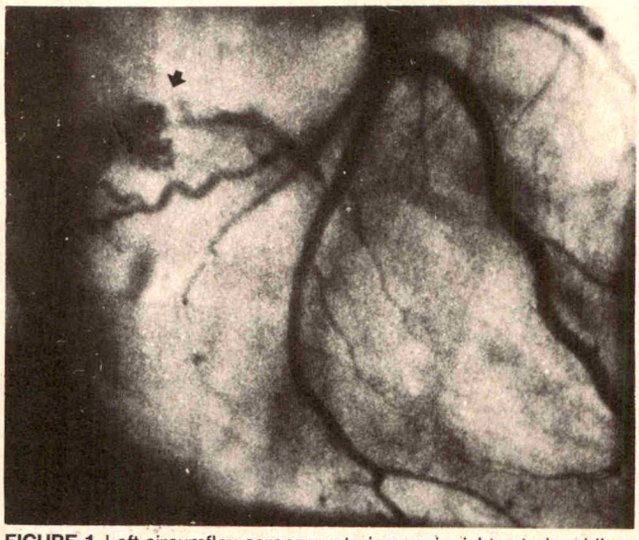

FIGURE 1. Left circumflex coronary arteriogram in right anterior oblique view. A large atrial branch divides into a cluster of small vessels (**arrow**).

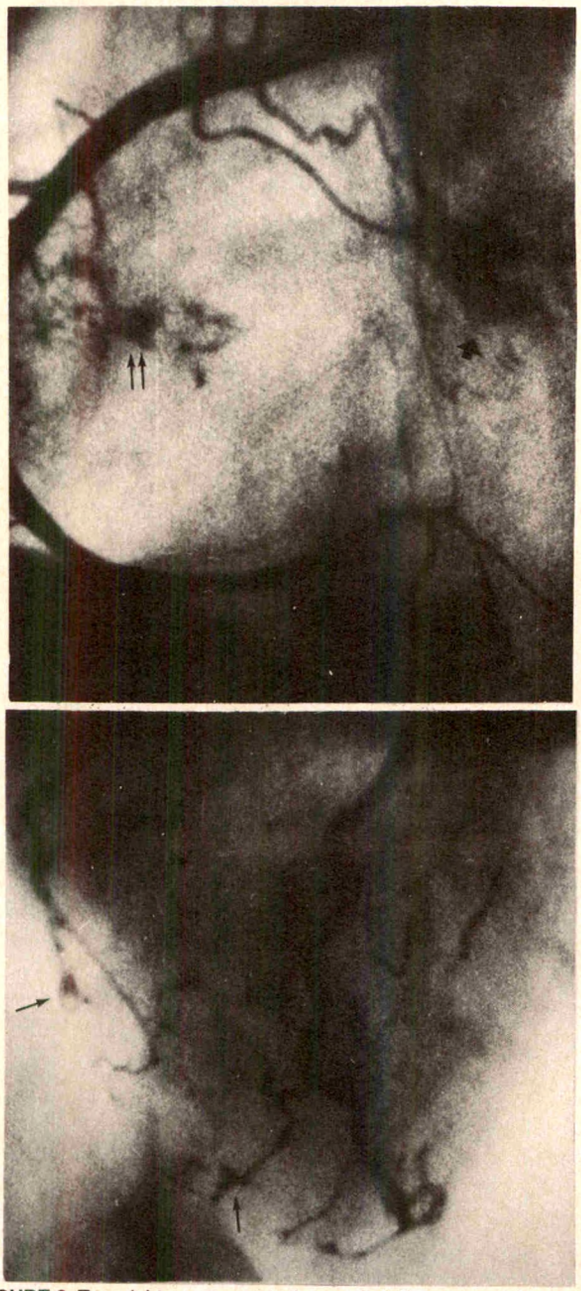

FIGURE 2. Top, right coronary arteriogram in left anterior oblique view. Note two abnormal clusters of vessels, the first originating from right ventricular branches (**wide arrow**), the second originating from left atrial branches (**two thin arrows**). **Bottom, left coronary arteriogram** in craniocaudal right anterior oblique view. Distal branches of both the left anterior descending and circumflex arteries show narrowings and aneurysmal dilatations (**arrows**).

4, top). In the base of the right ventricular myxoma a strikingly large number of vessels was found.

The tumor of the left thigh was extirpated. On histologic examination (Fig. 4, bottom), this also appeared to be a myxoma. No myxomatous tissue could be detected in the walls of the vessels of the subcutis. Vessel wall destruction was not observed. Reviewing the histologic preparations of the tumor removed from the subcutis of the right shoulder in 1974, we confirmed the diagnosis of myxoma.

Discussion

Sites of multiple tumors: Multichambered cardiac myxomas, usually located in both atria, have been reported several times. The occurrence of myxomas in the left and right ventricles was reported by DeMaria et al.[13] and in the left atrium and left ventricle by Morgan et al.[17] However, their occurrence in the left atrium and right ventricle has not previously been reported. The diagnosis of intracardiac tumor growth in our patient was made by demonstration on coronary arteriography of abnormal vessels supplying the tumor. This finding has rarely been described,[18–20] although myxomas are generally well vascularized.

There is no report, so far as we know, of a combination of intracardiac myxomas and myxomas located elsewhere in the body. We can only speculate as to a causal relation between the different sites. Price et al.[21] suggested the possibility of metastatic growth of myxomatous emboli. In our case we found no histologic evidence of a metastatic origin of the myxomas of the left thigh and right shoulder, but such a process cannot be entirely excluded.

Embolic complications: Frequently the first symptoms of myxoma originate from embolic complications. In two large series of postmortem cases reported by Mahaim[22] and Prichard,[23] embolization to peripheral arteries, lungs, kidneys and brain was relatively frequent. On a recent review of reported cases,[24] embolization was demonstrated in 45 to 60 percent of left-sided and in 8 to 10 percent of right-sided cardiac myxomas.

Electrocardiographic evidence of myocardial infarction, present in our patient, has frequently been noted in patients with cardiac myxoma. Myocardial infarction during surgical removal of a left atrial myxoma was noted and reported by Differding et al.[25] Chamberlin et al.[26] removed a tumor embolus from the left anterior descending artery during surgery for a left atrial myxoma. With these exceptions only postmortem evidence of coronary embolization from cardiac myxoma has been reported.[21,27,29] Price et al.[21] documented

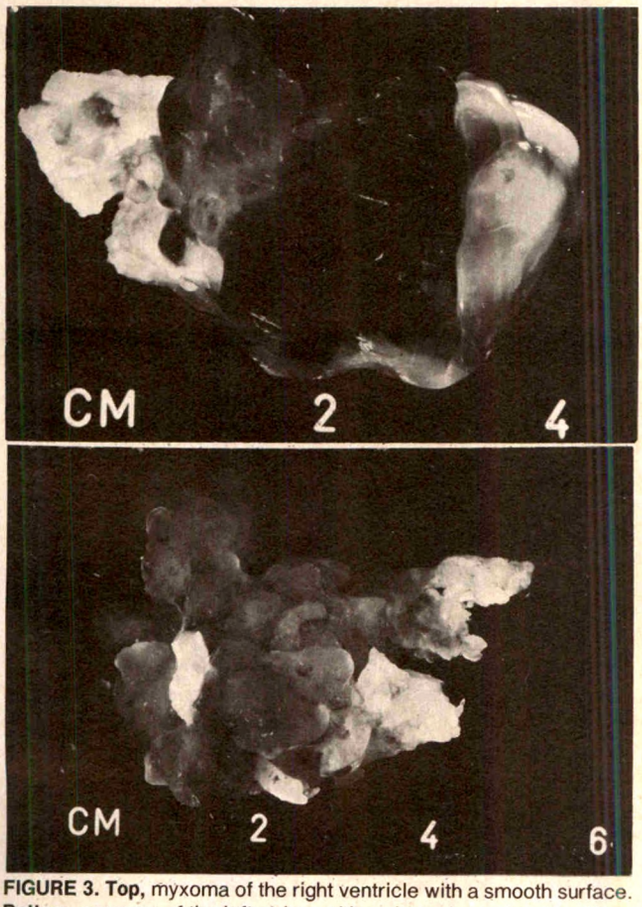

FIGURE 3. Top, myxoma of the right ventricle with a smooth surface. **Bottom,** myxoma of the left atrium with an irregular and partly villous aspect.

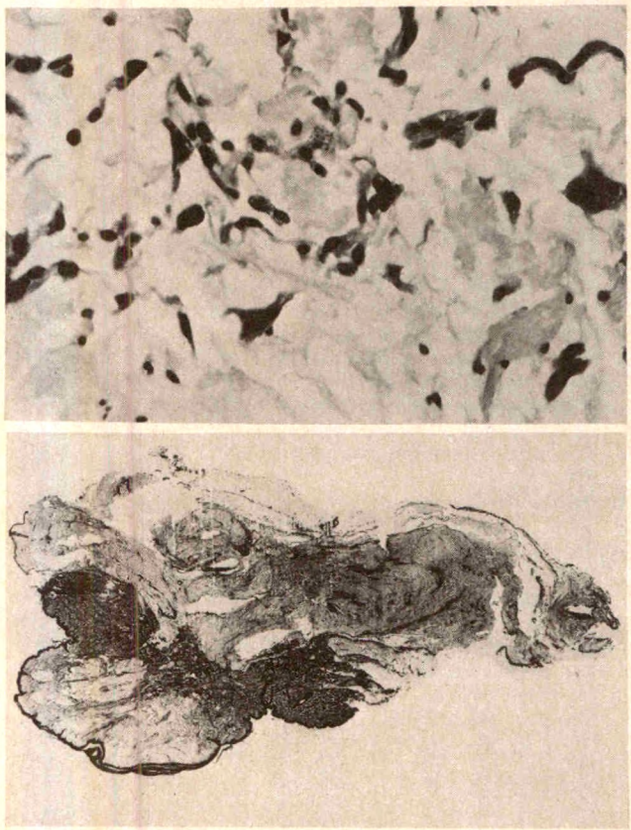

FIGURE 4. Top, microscopic appearance of the myxoma of the right ventricle. (Hematoxylin-eosin, ×350, reduced by 31 percent.) **Bottom,** light microscopic appearance of the dermal tumor of the left thigh with the characteristic structures of a myxoma. (Alcian Blue ×4, reduced by 31 percent.)

in one case that myxomatous emboli had partially destroyed the coronary as well as the cerebral arterial walls, resulting in aneurysmal dilatations.

We assume that the patient's neurologic symptoms preceding the myocardial infarction were caused by embolization to the cerebral vessels, although this could not be substantiated with carotid angiography. Similarly, we assume that the intermittent pains in the limbs were caused by ischemia due to embolization.

Angiographic findings: In our patient coronary arterial narrowings and aneurysmal dilatations were demonstrated at angiography. Similar abnormalities, proven to result from tumor emboli, have been observed in the cerebral vessels.[17,26,27,30–32] Leonhardt and Kullenberg[33] reported a case of bilateral atrial myxomas with multiple arterial aneurysms, located in the pulmonary, renal and cerebral arteries. We assume that in our case the arteriographic findings of the distal coronary branches were due to myxomatous emboli. This explains the occurrence of myocardial infarction in the absence of obstructive lesions in the larger coronary arterial branches. Ours is the first report to describe these unique angiographic findings.

Clinical implications: The occurrence of multiple tumor sites highlights the need to investigate further the metastatic behavior of myxomas. Because left-sided cardiac myxoma may produce coronary embolization, myxoma has to be excluded in cases of myocardial infarction without obstructive lesions in the major branches of the coronary arteries.

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LETTERS TO THE EDITOR

ASSESSMENT OF MEDICAL THERAPY OF ANGINA PECTORIS

As recently emphasized by critics of the Veterans Administration Cooperative Study of coronary artery disease,[1] the adequacy of medical and surgical treatment is of paramount importance in any study comparing these therapeutic alternatives. The quality of surgical treatment may be roughly measured in terms of operative mortality and bypass graft patency. The adequacy of medical pharmacotherapy with propranolol and long-acting nitrates is more difficult to assess. Propranolol is thought to relieve angina primarily by decreasing heart rate, especially by attenuation of the sympathetically mediated increase in heart rate during exercise,[2] and to a lesser degree by decreasing contractility. Although there is marked individual variation in propranolol dosage requirements,[3,4] reduction in clinical and electrocardiographic manifestations of myocardial ischemia correlates with achieving adequate beta adrenergic blockade.[5,6] To ensure a high degree of beta blockade one should ideally demonstrate a substantial reduction in heart rate during standardized exercise as compared with the control state.[2,4,5] As a minimum, patients treated with propranolol should have resting bradycardia.[2,6] In the recent report by Pugh and associates,[7] the data presented are inadequate to judge the degree of beta blockade in the medical group. Although exercise studies would have been inappropriate in patients with unstable angina, resting heart rates are not given and the mean propranolol dose (140 mg/day) is lower than the average of 160 to 240 mg/day required for adequate beta adrenergic blockade in most subjects.[6]

The major effects of long-acting nitrates are qualitatively identical to those of nitroglycerin.[8] These agents are thought to be beneficial in ischemic heart disease primarily by decreasing preload and afterload, and thereby favorably altering the relation between myocardial oxygen supply and demand.[9] There is considerable individual variability in the dose of long-acting nitrates required to achieve these hemodynamic effects.[8,10,11] Although there is no measure of preload that is both convenient and inexpensive, afterload can be approximated clinically by the arterial blood pressure. It has been suggested that a 10 mm decrease in upright systolic blood pressure can be used as evidence of altered hemodynamics resulting from long-acting nitrates.[8] Pugh et al. do not provide such data, and the mean dose of oral isosorbide dinitrate in their medical group (40 mg/day) is at the lower end of the therapeutic spectrum. The importance of administering long-acting nitrates in adequate dosage has been emphasized,[11] and most studies demonstrating sustained hemodynamic effects from long-acting nitrates have used individual doses of 20 to 50 mg every 6 hours.[11–13]

These considerations make it impossible to assess the adequacy of therapy in the medical group of Pugh et al., and constitute a major limitation of their report.

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REPLY

We are in complete agreement with Bauman's statements. The patients presented in our report were maximally medically treated in the sense that the individualized dose of propranolol was the maximal one a particular patient could tolerate. The same applies to the dose of isosorbide dinitrate utilized.

Although one does wish to use as large a dose of each of these agents as possible, side effects may limit the amount of each agent that is given. Specifically, headaches may develop in patients receiving isosorbide dinitrate, and in our experience this often limits the maximal dose of this agent that one can deliver. Propranolol may slow heart rate to levels below which one would prefer not to go, result in increased fatigability, influence the degree of left ventricular failure that is present, and so forth. Each patient who received propranolol did have a significant reduction in resting heart rate. However, the important point is that the medical regimen utilized in this study was individually tailored to be maximal and medically appropriate for the particular individual being treated.

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PACEMAKER SYNDROME

Alicandri et al.[1] described three cases of hypotension with ventricular pacing. Similar cases have previously been reported.[2,3]

Case 1: We were able to study a patient with an extreme decrease in blood pressure after right ventricular pacemaker implantation.[4] After operation, a synchronization with isorhythmic dissociation developed with a periodic decrease in

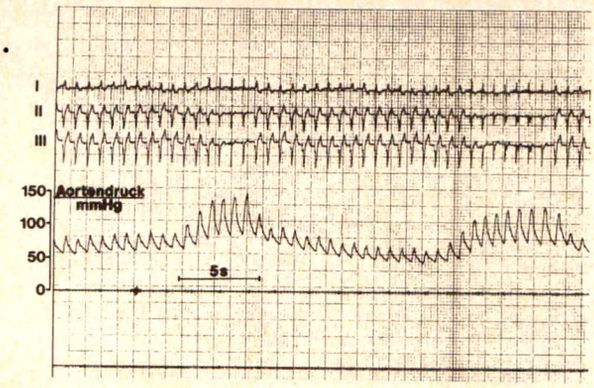

FIGURE 1. Periodic decrease in aortic pressure (**bottom,** Aortendruck) due to atrial-ventricular dissociation caused by isorhythmic dissociation. In electrocardiographic leads I to III (**top**) the change in P waves can be observed.

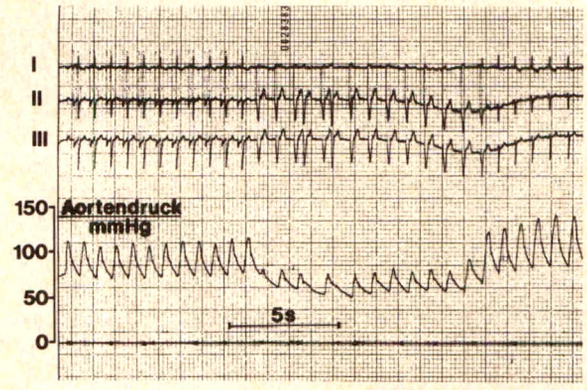

FIGURE 2. From left to right, sequential atrial-ventricular pacing, ventricular pacing and sinus rhythm can be observed. Ventricular pacing leads to a reduction in blood pressure. The coordinate atrial-ventricular contraction in sinus rhythm at right is followed by an overshoot in aortic pressure.

blood pressure when the heart was stimulated by the pacemaker (Fig. 1, top). This was accompanied by a change in the color of the skin; periodically a hyperemic red color or white skin could be observed. Cardiac index (2.6 liters/min per m^2) and aortic pressure (110/70 mm Hg) were equal during sinus rhythm and atrial and sequential atrial and ventricular pacing. During ventricular pacing, cardiac index decreased to 1.7 liters/min per m^2 and aortic pressure to 70/50 mm Hg (Fig. 2). The pacemaker was explanted because of the hemodynamic situation. It was decided not to implant an atrial-stimulating or sequential pacemaker because of the good conduction and rhythm of the patient which was examined electrophysiologically.

Case 2: Another patient studied after implantation of a ventricular pacemaker had a decrease in left ventricular pressure from 105 to 80 mm Hg. Cardiac index also decreased from 4.1 to 2.8 liters/min per m^2. In Germany we call this phenomenon Schrittmacher syndrom (pacemaker syndrome).

Raimund Erbel, Dr Med
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REPLY

We welcome the confirmation of our observations by Erbel and his colleagues. We were not familiar with the German journals cited, and Karlöf's study did not really refer to the subject under discussion, but rather to cardiac performance levels. Calculation of systemic vascular resistance from data in Erbel's letter demonstrates the same findings as in our patients, namely, a practically unchanged total peripheral resistance (33 versus 32 units during effective atrial contraction) despite a 35 percent reduction in cardiac index. Obviously the significant hypotension observed in these patients must be related to some interference with normal compensatory reflexes that limit the decrease in arterial pressure in most patients. The term "pacemaker syndrome" is appealing but possibly somewhat restrictive because a similar pattern can develop with any atrioventricular dissociation.

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LIDOCAINE AND INFARCTION

Although I agree with many of their conclusions, I would like to correct some errors in the paper by Lazzara et al.[1] concerning the work we had initiated on the electrophysiologic effects of lidocaine and other agents in infarcted and normal zones[2,3] and on the interaction between abnormal and normal zones. The authors indicate that in Figure 1 of Kupersmith et al.[3] there "apparently was little delay in conduction." This is true; however, Figure 1 was an illustrative example and the new data on conduction in Figure 2 did not indicate the extent of delay induced by infarction. Also shown in Figure 2 was the fact that lidocaine selectively prolonged refractoriness in the infarcted zone, which is an important effect and one that could certainly curtail arrhythmias. Lazzara et al. did not mention this observation, although they included a lengthy discussion of refractoriness and its importance in antiarrhythmic effects. Second, our study was not concerned with the effect of lidocaine on ischemia but rather with its effects on infarction. The study was performed from 2 to 6 hours after coronary arterial ligation in each dog and at this time arrhythmias do not occur.[4] As is well known, arrhythmias occur very early after coronary arterial ligation. In another study[5] we examined the effects of lidocaine in the first 15 minutes after coronary arterial ligation and found that it curtailed arrhythmias (that is, reduced the frequency of ventricular complexes), slowed conduction and prolonged refractoriness in the ischemic zone and reduced the disparity in monophasic action potential duration between zones. Thus certain electrophysiologic properties of lidocaine are correlated with antiarrhythmic properties.

The problem of which electrophysiologic effects might cause a reduction of arrhythmias is a difficult one. Delay of conduction can at times curtail and at other times promote arrhythmias. Based on work over the years in models in which electrophysiologic and antiarrhythmic effects are correlated[5–10] with a variety of agents, we can say that is clear that effects on conduction alone do not explain antiarrhythmic properties, that prolongation of conduction if it is the only electrophysiologic effect of an agent can promote arrhythmias, and that effects on the interplay of action potential duration and effective refractory period between ischemic and normal zones are important in curtailing reentrant arrhythmias.[6] For example, both lidocaine[5,6] and propranolol[7] curtail arrhyth-

mias and prolong conduction selectively in the ischemic zone; also these agents prolong effective refractory periods in the ischemic zone and reduce the disparity in monophasic action potential duration between zones. Verapamil,[10] on the other hand, when administered after ligation, prolongs conduction, has no effect on action potential duration or effective refractory period and promotes arrhythmias.

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REPLY

Although we have read Kupersmith's letter carefully, we are unable to pinpoint any specific errors, but we do agree with him that certain interpretations and conclusions of ours differ from those that he had derived. The first point that he makes concerning the delay of conduction in his studies confused us. We are not sure whether conduction was or was not markedly delayed in some of his experiments. We stand by our statement that in the one example that he showed, it was not markedly delayed.

He also made the point that we failed to refer to his data showing "prolongation of refractoriness" by lidocaine in the ischemic tissues. In fact, his data show a restoration of a shortened refractoriness toward normal. This is indicated by Figure 3, in which the difference in the refractory periods between the normal and infarct zone approached 0 with lidocaine administration. It appears that refractoriness was mildly shortened in the ischemic zone (about 20 to 25 percent) before the administration of lidocaine and lidocaine corrected this shortening. We are not certain of the importance of mild shortening of refractoriness in the initial generation of ectopic activity. Kupersmith apparently believes that differences in refractoriness of this magnitude are important in the genesis of arrhythmias. This is a point of difference in interpretation between us and him. We agree that disparity in refractoriness might be a factor in *sustaining* arrhythmias or in degeneration into ventricular fibrillation. Our discussion emphasized the marked absolute prolongation of refractoriness produced in severely affected tissues by lidocaine. This pronounced prolongation of refractoriness was a factor in the failure of ischemic tissues to respond after lidocaine administration. We concluded that the extinguishment of responses of severely depressed tissues was a major factor in the antiarrhythmic effect in our model. Kupersmith in the last paragraph of his letter focuses more on delay of conduction whereas our focus was on *abolition* of conduction. Since we covered this in some detail in our paper, we will not belabor it here. We consider that the effect of prolonging conduction by an agent is of uncertain significance in terms of suppressing arrhythmias.

Kupersmith states that his study was "not concerned with the effect of lidocaine on ischemia but rather its effect on infarction." This is probably a semantic disagreement but we believe that he was studying the effects on ischemic but viable tissues.

We recognize that Kupersmith and his co-workers took an important step in focusing on abnormal tissues in the studies of the mechanisms of antiarrhythmic drugs. The added value of our studies, if any, has been to narrow the focus somewhat to those abnormal tissues that are in fact generating arrhythmias and those specific electrophysiologic derangements that are instrumental in the generation of arrhythmias—that is, marked conduction defects, abnormal automaticity, and so forth. We do not believe that our concepts and those of Kupersmith and his co-workers are greatly at odds, but we do believe that the specific model they chose for study in their series of experiments was not the most advantageous because of the lack of arrhythmias.

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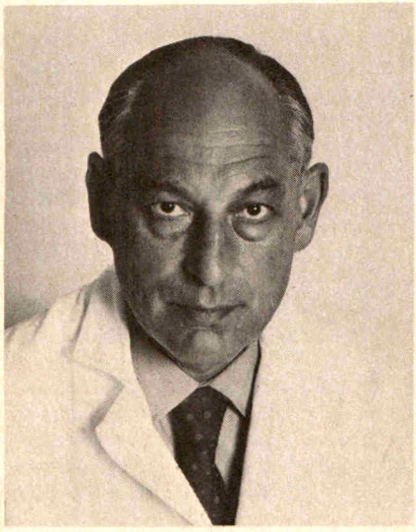
PRESIDENT'S PAGE:

The Ambience of Heart House



Borys Surawicz, MD, FACC

The Heart House is an architecturally pleasing, comfortably laid-out brick and glass structure, built on a tastefully landscaped, spacious, wooded lot that shields it from the traffic noise of Bethesda's Old Georgetown Road. The property is owned by the membership of the American College of Cardiology. Our house has been paid for in full and, perhaps it is worth mentioning, without the use of a single federal, state or municipal tax dollar.

The Heart House was created primarily to accommodate our administrative headquarters and to serve as the site of our unique teaching laboratory, known as the Learning Center. In accordance with these plans, the everyday life of Heart House is dominated by the educational activities on the first floor and the administrative activities of our staff on the second floor. But I believe that a visitor inclined to do a bit of browsing will perceive that the stylish and elegant interior is quite different from the customary milieu of a traditional classroom or an office suite. The premises seem conducive to social and artistic functions. It is not surprising that Heart House has witnessed many interesting events unrelated to the business of administration and continuing education. Since they probably are least well known to our membership, here is a brief account of those activities. I have received from our Executive Director, Mr. William (Bill) Nelligan, the list of happenings and events labeled by him as the "third dimension" items. They seem to fall into several categories:

1. *Heart House is a popular meeting place.* Various committees of the National Heart, Lung, and Blood Institute, most notably the U.S.-U.S.S.R. Steering Committee have held their meetings here. The U.S. Food and Drug Administration chose Heart House for a Tripartite Conference that included representatives from Canada and the United Kingdom. Heart House also hosted meetings of the American Red Cross, Bethesda Rotary Club, American Society of Association Executives and Montgomery County Heart Association.

2. *Heart House is a showcase.* The Office of International Affairs, which manages various exchange programs of the National Heart, Lung, and Blood Institute, has brought cardiologists from Hungary, Poland, U.S.S.R. and other Socialist countries to show them an example of a voluntary-membership medical specialty society supported by private funds. A team from the Japan Society of Medical Education visited us to gather data and ideas for a proposed biomedical communications center in their country. Of the domestic organizations, the American Pharmaceutical Association sent staff representatives seeking ideas for expansion of their continuing education efforts, and the National Library of Medicine staff visited us on several occasions in conjunction with the planning for the new Lister Hill facility, which is now under construction. The National Library of Medicine had also requested tours for visitors from Japan, India and the U.S.S.R. Notable visitors to Heart House included the director of professional education of the Canadian Heart Association, and continuing education specialists from the American College of Radiology, the American Society of Clinical Pathologists and the American College of Obstetricians and Gynecologists.

3. *Heart House is an exhibit site.* The Museum of Electricity in Life established by Mr. Earl Bakken, co-founder of Medtronic Inc. in Minneapolis, mounted two exhibits in Heart House. The first, which was prepared for our Dedication, was entitled "Early Electrocardiography," and the second, installed in June 1979, features the history of cardiac pacing.

4. *Permanent collections are maintained in Heart House.* A historical collection of stethoscopes was presented to the College by Drs. E. Grey Dimond and the late Paul Dudley White. The stethoscopes include specimens manufactured and used during the past two centuries in China, Japan, Russia, Germany, France and many other countries. Dr. Dimond also made available the display cases housing the stethoscopes.

5. *Gifts of furniture and rare books have been presented to Heart House.* In the Paul Dudley White Room are located the desk and other memorabilia from Dr. White's study, donated to Heart House by his widow. A hand-carved camphorwood chest, a repository of rare books presented by Dr. and Mrs. Hans Tang of Hong Kong, came to us from Asia, as did a narra wood conference room table donated by the Philippine membership of the American College of Cardiology, and a book of Chinese archaeological treasures presented by the delegation of Chinese cardiologists who visited Heart House on November 10, 1978.

6. *Gifts of art have been presented to Heart House.* Near the front entrance to Heart House, you will see a 16 foot sculpture entitled "Man Helping Man." It

was donated by our immediate past president, Dr. Leonard S. Dreifus, and his wife, Seline, and was dedicated in a ceremony on May 6, 1979. The sculptor, Mr. Harold Kimmelmann, of Philadelphia, expressed the fundamental idea of human dedication to noble purposes in a statue of a tree stump climbed by two boys, one extending his helping hand to the other. It is obvious that Len and Seline commissioned the attractive sculpture as a symbol of the humanitarian ideals guiding our College.

It is clear that Heart House has already captured the imagination of many non-College members in this country and abroad. We have witnessed activities that extend the role of Heart House beyond the scope of the Learning Center and the administrative headquarters of the College. What we need now is to increase the involvement of our membership in the expansion of the "third dimension" activities. The creativity and imagination of the College members will determine how our home in Bethesda will be used in the future. It is a logical place for reunions with former colleagues and teachers or meetings with foreign visitors. The talents of our members could be expressed in the exhibits of their photography or art works. The splendid acoustics of our classroom could be conducive to musical events staged by our members. Some of our collectors may wish to loan their privately owned works of art for occasional exhibits.

Sturdy buildings span lives of many generations. We have in this country the first building created by cardiologists for the use of cardiologists. It should be enjoyed by our contemporaries and passed on to our successors as an inspiring monument to our strivings and achievements.

Borys Surawicz, MD, FACC
President
American College of Cardiology

29TH ANNUAL SCIENTIFIC SESSION

AMERICAN COLLEGE OF CARDIOLOGY

HOUSTON, TEXAS MARCH 9 TO 13, 1980

CALENDAR OF EXTRAMURAL PROGRAMS

The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the National Committee of Continuing Education assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The National Program Committee for Continuing Medical Education of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Leonard S. Dreifus, MD, FACC
Chairman, Continuing Education Committee for Extramural Programs

Programs and faculty are subject to change. For further information write Registration Secretary, Extramural Programs Department, American College of Cardiology, Heart House, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

OCTOBER 1979 THROUGH MARCH 1980

To be arranged individually — **Preceptorships in Cardiology.** Arthur Seizer, FACC, director, Pacific Medical Center, San Francisco, CA

To be arranged individually — **Preceptorships in Cardiology.** Jules Constant, FACC, director. Buffalo General Hospital, Buffalo, NY

OCT. 11–13 — **New Concepts in Management of Congestive Heart Failure.** Peter C. Gazes, FACC, director and Charles P. Summerall, III, FACC, Grady H. Hendrix, FACC, William H. Barnwell, II, FACC, Bruce W. Usher, FACC, J. Lindsay Leviner, FACC, Robert G. Irvin and Larry E. Kibler, co-directors. Kiawah Island Inn, Kiawah Island, Charleston, SC

OCT. 18–20 — **Cardiology Update—1979.** William W. Parmley, FACC and Kanu Chatterjee, FACC, directors. Del Monte Hyatt House, Monterey, CA

OCT. 22–23 — **Correlations in Ischemic Heart Disease.** Leonard S. Gettes, FACC, director. Carolina Inn, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC

OCT. 25–27 — **New Techniques and Concepts in Cardiology. Coronary Artery Disease: Rehabilitation, Surgery, Coronary Spasm, Balloon Dilatation; Valvular Heart Disease; Hypertrophic Cardiomyopathy.** Stephen E. Epstein, FACC, director. Hyatt Regency Hotel, Washington, DC

NOV. 5–14 — **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC and James E. Crockett, FACC, directors. Rancho Santa Fe Inn, Rancho Santa Fe, CA

DEC. 2–5 — **Coronary, Valvular, Hypertensive and Myocardial Heart Diseases: The Multi-disciplinary Approach.** William C. Roberts, FACC, director. Williamsburg Conference Center, Williamsburg Lodge, Williamsburg, VA

DEC. 7–9 — **Advances in Heart Disease 1980.** Dean T. Mason, FACC, director. Fairmont Hotel, San Francisco, CA

DEC. 12–14 — **Cross-Sectional Echocardiography vs. Cardiac Nuclear Imaging.** Joel Morganroth, FACC, director. Fairmont Hotel, Philadelphia, PA

DEC. 14–16 — **Twelfth Annual Cardiovascular Symposium: Clinical Decisions in Cardiovascular Disease.** Henry I. Russek, FACC, director. Sheraton Centre, New York, NY

1980

JAN. 14–18 — **Eleventh Annual Cardiovascular Conference at Snowmass.** John H. K. Vogel, FACC, director and Bruce C. Paton, FACC, co-director. Snowmass Resort, Snowmass, CO

JAN. 15 — **Coronary Artery Disease: Diagnosis and Treatment.** William C. Sheldon, FACC and J. Kent Trinkle, directors. Convention Center, San Antonio, TX

JAN.31–FEB. 2 — **Fundamentals of Echocardiography—An Introductory Course for Clinicians.** Joseph K. Perloff, FACC, director and Pravin M. Shah, FACC and John S. Child, FACC, co-directors. Century Plaza Hotel, Los Angeles, CA

FEB. 13–15 — **Cardiac Diagnosis: Reappraisal of Established Techniques and the Place for New Techniques.** Ralph Shabetai, FACC, John Ross, Jr., FACC, Gabriel Gregoratos, FACC and Joel S. Karliner, FACC, directors. Vacation Village Hotel, San Diego, CA

MAR. 24–28 — **Thirteenth Annual Seminar on Electrocardiographic Interpretation of Complex Arrhythmias: A Physiological Approach.** Charles Fisch, FACC and Douglas P. Zipes, FACC, directors. Indianapolis University Medical Center, Indianapolis, IN

.EARNING CENTER: PROGRAM CALENDAR

he American College of Cardiology's newest department, the Learning enter, located at the College's Bethesda Maryland headquarters, began perations in October 1977 with the offering of its first continuing ıedical education program for physicians with a specialty or an interest ı cardiovascular medicine. The purpose of the Learning Center is to ıpport the professional commitment to quality patient care by providing a new standard of excellence in cardiovascular continuing education. For additional information concerning the programs listed below or for a complete schedule of programs through December 1979, contact Program Coordinator, Learning Center, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20014. Telephone (301) 897-5400.

OCTOBER 1979 THROUGH MAY 1980

Month/Dates	Program Director	Title of Program
ct. 8–11	Leonard S. Dreifus, MD	Mechanisms and Therapy of Cardiac Arrhythmias
ct. 15–17	Marvin Moser, MD	Hypertension
ct. 29–31	Max Harry Weil, MD	Emergency Care of the Critically Ill Patient
ov. 1–3	Barrie Levitt, MD	Cardiovascular Therapeutics
ov. 28–30	William W. Parmley, MD	Non-Invasive Cardiovascular Procedure: Principles and Clinical Application
an. 21–24	William C. Roberts, MD	Congenital Heart Disease
an. 28–30	Gottlieb Friesinger, MD	Coronary Artery Surgery
eb. 6–8	Bertram Pitt, MD	Nuclear Cardiology
eb. 13–15	Melvin L. Marcus, MD	New Approaches to the Short and Long Term Treatment of Myocardial Infarction
eb. 18–20	Roger A. Winkle, MD	Antiarrhythmic Therapy: Current Status and Future Promise
arch 24–26	John A. Mantle, MD	Quality Assurance and Management for Cardiovascular Nurses
arch 27–29	John Spittell, MD	Peripheral Vascular Disease
pril 9–11	Victor Parsonnet, MD	Current Concepts in Pacing
pril 14–16	Keith Cohn, MD	Exercise Testing
pril 21–23	Nanette Wenger, MD	Cardiac Rehabilitation
pril 28–30	Pravin M. Shah, MD	M-Mode and 2-Dimensional Echocardiography: Current Status and Future Promise
lay 1–3	Daniel S. Berman, MD	Nuclear Cardiology
lay 5–7	Robert G. Tancredi, MD	Pulmonary, Renal and Electrolyte Considerations in Cardiovascular Disease
lay 12–14	Louis Lemberg, MD	CCU Update for Nursing Supervisors
lay 19–21	Arthur E. Weyman, MD	Cross-Sectional Echocardiography

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31. Vismara LA, Vera Z, Miller RR, Mason DT: Efficacy of disopyramide phosphate in the treatment of refractory ventricular tachycardia. Am J Cardiol 39:1027–1034, 1977

(Author: please note that no periods are used after authors' initials.)

For books (edited by other than author of article):

28. Schiebler GL, Van Mierop LHS, Krovetz LJ: Diseases of the tricuspid valve, chap 20. In, Heart Disease in Infants, Children and Adolescents (Moss AJ, Adams F, ed). Baltimore, Williams & Wilkins, 1968, p 134

For books (with identical author and editor):

36. Berne E: Principles of Group Treatment. New York, Oxford University Press, 1966, p 26

(Author: all book references should have specific page numbers.)

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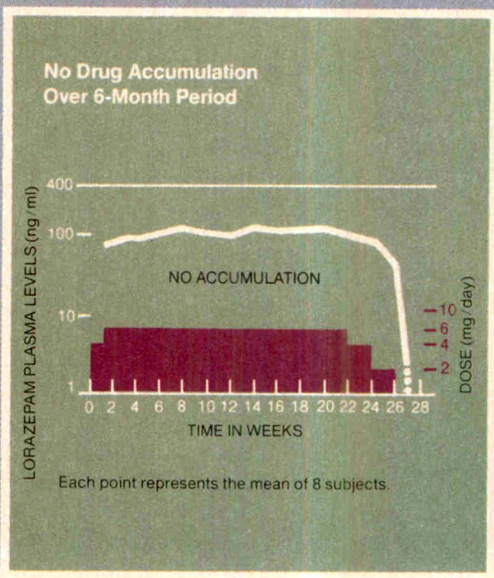
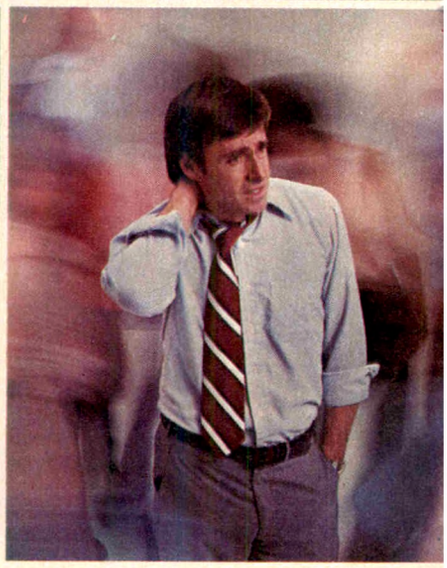
How do you choose a minor tranquilizer?





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Pharmacokinetics

Ativan (lorazepam) is eliminated more rapidly than other benzodiazepines; generates no clinically active metabolites. The half-life of free lorazepam is about 12 hours; steady-state blood levels are attained in 2-3 days. (Comparable data for diazepam: 20-50 hours and at least 7-10 days.) Ativan shows no evidence of accumulation, even when given in high doses for as long as 6 months. (The pharmacokinetic profile of a drug can define such characteristics as absorption, distribution, metabolism and elimination but cannot, at present, be directly related to its therapeutic effectiveness.)

Anxiety neuroses

In many nationwide studies involving thousands of patients with anxiety neuroses, Ativan (lorazepam) consistently provided significant relief of anxiety, tension, agitation and irritability as measured by standard Hamilton, Global (physician rated) and 35-Item (patient self-rated) scales.

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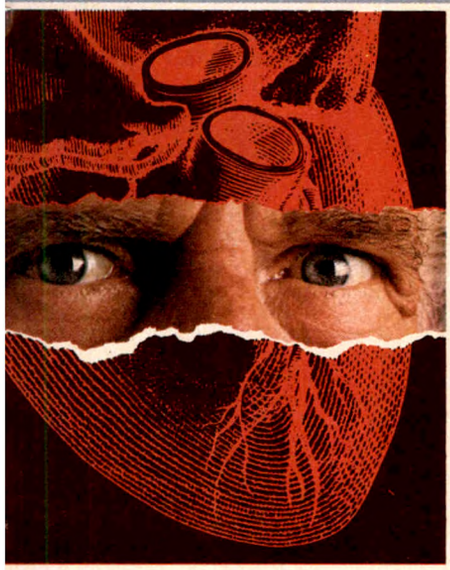
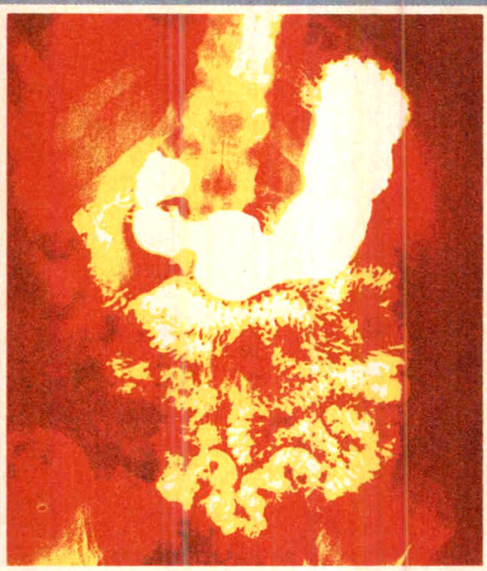
They're all about the same, aren't they? Until recently, that seemed to sum up the prevalent attitude about the benzodiazepines. After all, they all work similarly and all are effective anxiolytics. With seven of these compounds now available, however, differences have begun to emerge. Foremost among them: different metabolic pathways, which distinguish the relatively short-acting Ativan (lorazepam) from long-acting diazepam, clorazepate and chlordiazepoxide. At the same time, your choice can be made with confidence in the clinical record of Ativan, which confirms its value in anxiety neuroses and in significant anxiety associated with functional or organic disorders, as well as in older patients.

Consider the record of Ativan:



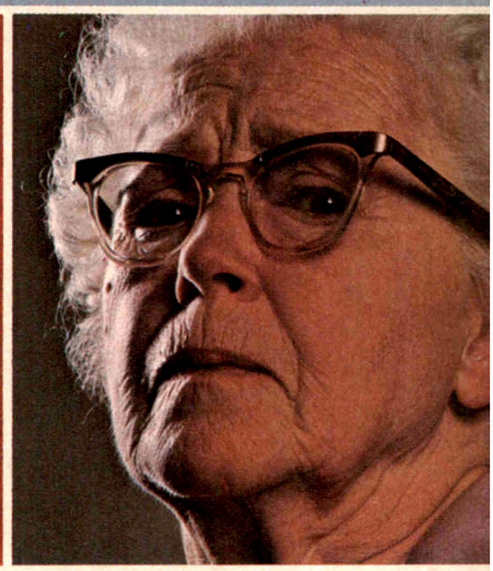
Anxiety in cardiovascular disorders

Ativan (lorazepam) has been specifically evaluated and found effective in seven common protocol, double-blind studies involving 423 patients (211 on Ativan) whose anxiety was related to organic and functional cardiovascular disorders. The cardiovascular component has not, of course, been shown to be significantly benefited by such therapy.



Anxiety in gastrointestinal disorders

So far, nine common protocol, double-blind studies of Ativan have focused on anxious patients with functional or organic gastrointestinal complaints (457 patients, 234 on Ativan). Ativan was clearly effective in reducing the anxiety of these patients. The gastrointestinal component has not, of course, been shown to be significantly benefited by such therapy.



Anxiety in the aging patient

Because its simple metabolism is not readily impaired with advancing age, and accumulation is not likely to present a problem, Ativan is a good choice for older patients. Those who have trouble swallowing solid medication appreciate the small Ativan tablet, which is tasteless and disintegrates within seconds in water or fruit juice.

Ativan® (IV) for (lorazepam) Anxiety

See important information on following page.

Brief Summary of Prescribing Information

Indications and Usage: Symptomatic relief of anxiety, tension, agitation, irritability and insomnia associated with anxiety neuroses and transient situational disturbances; anxiety associated with depressive symptoms and as a treatment of symptoms of anxiety if such symptoms are a significant feature of functional or organic disorders, particularly gastrointestinal or cardiovascular.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients on lorazepam not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation.

Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions.

Observe usual precautions with impaired renal or hepatic function.

Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component.

Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (approximately 6 times the maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatric patients requires caution and frequent monitoring for symptoms of upper G.I. disease.

Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug.

In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind that multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring of vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® IV for (lorazepam) Anxiety

Dosage: **Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.**

How Supplied: **0.5, 1.0 and 2.0mg tablets.**

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Quantitative MB/CPK results STAT any time of day or night

Know without delay whether myocardial infarction has occurred. The new Lancer MB/CPK Separation System ends your long wait for isoenzyme information while providing **quantitative** results to aid in a more accurate diagnosis.

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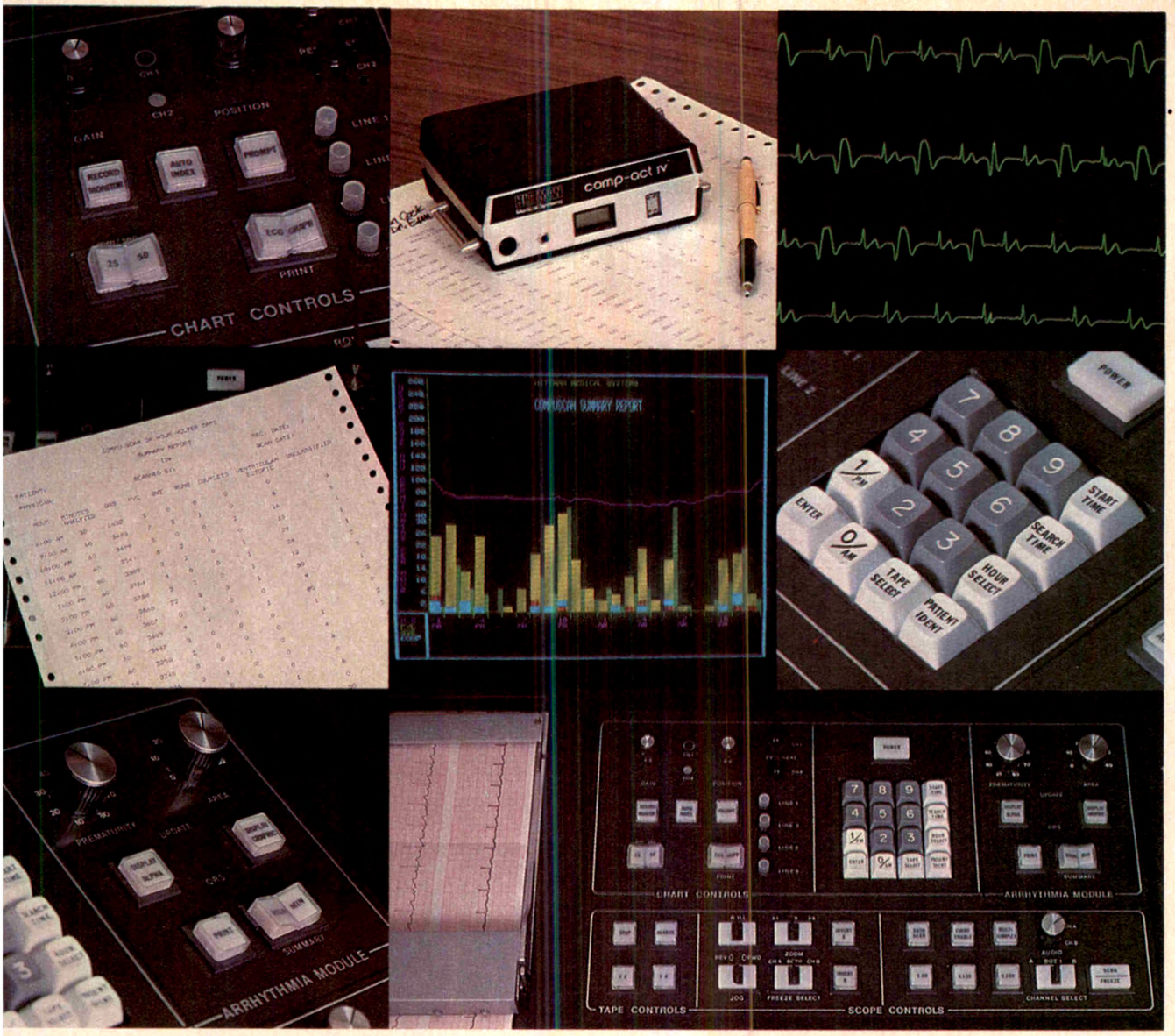

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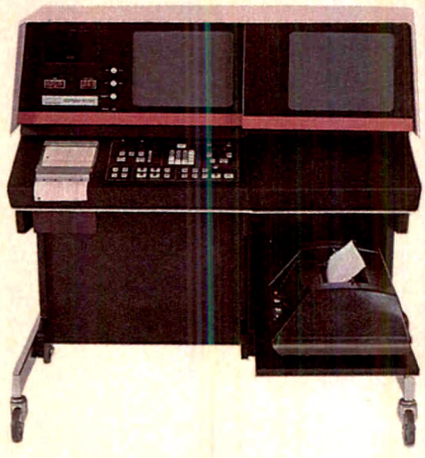

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An
Inotropic Agent
for the Short-Term
Treatment of Low-Output
Cardiac Failure

Dobutrex®
Dobutamine HCl

Selectively Increases
Myocardial Contractility
with Consistent
Hemodynamic Improvements

See third page for brief summary of prescribing information.

Distinguishing Qualities of Dobutrex

Strong Inotropic Activity through Selective Stimulation

Dobutrex is a potent, positive inotropic agent whose primary activity results from stimulation of the β receptors of the myocardial muscle cells.[1]

Hemodynamic Improvements

Dobutrex has minimum effect on the adrenergic receptors in the vasculature.[1] In most patients, blood pressure changes are small, and decreases in afterload and preload have been reported in clinical investigations (see warnings).[2]

Small Effect on Heart Rate and Automaticity

Dobutrex has minimum effect on ventricular automaticity[3] and does not reduce blood pressure.[4] This, together with its low chronotropic potential, reduces the risk of arrhythmia (see warnings).

Renal Output and Urine Flow

Dobutrex does not have the direct renal vasodilative effect of low-dose dopamine; however, in patients with heart failure, Dobutrex generally promotes a diuresis as renal perfusion rises with the increased cardiac output.[5]

Direct-Acting

Unlike dopamine, Dobutrex acts directly on the myocardium and does not depend on the release of endogenous norepinephrine for its inotropic activity.

Myocardial Oxygen Balance

Increases in coronary heart perfusion due to increased cardiac output, together with a favorable influence on some of the major determinants of oxygen consumption (for example, decreases in left-ventricular filling pressure, decreases in systemic vascular resistance, and a mild chronotropic effect [2,6]), suggest that Dobutrex improves or maintains myocardial oxygen balance.

Infrequent Side Effects

Increases in heart rate, blood pressure, and ventricular ectopic activity have occurred. The drug is contraindicated in patients with idiopathic hypertrophic subaortic stenosis. In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used before therapy with Dobutrex is instituted. For warnings, precautions, and adverse reactions, see the brief summary of prescribing information.

Because of the rapid onset and brief duration of action of Dobutrex, precise adjustment of cardiac stimulation is possible by regulation of the rate of administration. As a result, when undesirable effects arise, temporary discontinuation of the infusion or reduction in dosage will generally reverse the adverse conditions. No additional remedial measures are usually necessary.

References:
1. Circ. Res., 36:195, 1975.
2. Circulation, 55:375, 1977.
3. Anesthesiology, 44:281, 1976.
4. Intensive Care Med., 3:57, 1977.
5. Circulation, 56:468, 1977.
6. Br. Heart J., 37:629, 1975.

Dobutrex® Lilly

Dobutamine HCl

For I.V. Injection
250 mg* in 20-ml vials
*Equivalent to dobutamine

Please see following page for brief summary of prescribing information.

Eli Lilly and Company
MC-897
P.O. Box 618
Indianapolis, Indiana 46206

Please send me additional information regarding Dobutrex® (dobutamine hydrochloride, Lilly).

Name

Address

City

State Zip Code

900923

Dobutrex®
Dobutamine HCl

Brief Summary
Consult the package literature for prescribing information.

Indications and Usage: Dobutrex® (dobutamine hydrochloride, Lilly) is indicated when parenteral therapy is necessary for inotropic support in the short-term treatment of adults with cardiac decompensation due to depressed contractility resulting either from organic heart disease or from cardiac surgical procedures.

In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to instituting therapy with Dobutrex.

Contraindication: Dobutrex is contraindicated in patients with idiopathic hypertrophic subaortic stenosis.

Warnings: 1. *Increase in Heart Rate or Blood Pressure*—Dobutrex may cause a marked increase in heart rate or blood pressure, especially systolic pressure. Approximately 10 percent of patients in clinical studies have had rate increases of 30 beats/minute or more, and about 7.5 percent have had a 50-mm Hg or greater increase in systolic pressure. Reduction of dosage usually reverses these effects promptly. Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation are at risk of developing rapid ventricular response. Patients with preexisting hypertension appear to face an increased risk of developing an exaggerated pressor response.

2. *Ectopic Activity*—Dobutrex may precipitate or exacerbate ventricular ectopic activity, but it rarely has caused ventricular tachycardia.

Precautions: 1. **During the administration of Dobutrex, as with any adrenergic agent, ECG and blood pressure should be continuously monitored. In addition, pulmonary wedge pressure and cardiac output should be monitored whenever possible to aid in the safe and effective infusion of Dobutrex.**

2. Hypovolemia should be corrected with suitable volume expanders before treatment with Dobutrex is instituted.

3. Animal studies indicate that Dobutrex may be ineffective if the patient has recently received a beta-blocking drug. In such a case, the peripheral vascular resistance may increase.

4. No improvement may be observed in the presence of marked mechanical obstruction, such as severe valvular aortic stenosis.

Usage Following Acute Myocardial Infarction—Clinical experience with Dobutrex following myocardial infarction has been insufficient to establish the safety of the drug for this use. There is concern that any agent which increases contractile force and heart rate may increase the size of an infarction by intensifying ischemia, but it is not known whether dobutamine does so.

Usage in Pregnancy—Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility, harm to the fetus, or teratogenic effects due to dobutamine. However, the drug has not been administered to pregnant women and should be used only when the expected benefits clearly outweigh the potential risks to the fetus.

Pediatric Use—The safety and effectiveness of Dobutrex for use in children have not been studied.

Drug Interactions—There was no evidence of drug interactions in clinical studies in which Dobutrex was administered concurrently with other drugs, including digitalis preparations, furosemide, spironolactone, lidocaine, glyceryl trinitrate, isosorbide dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid, and acetaminophen. Preliminary studies indicate that the concomitant use of dobutamine and nitroprusside results in a higher cardiac output and, usually, a lower pulmonary wedge pressure than when either drug is used alone.

Adverse Reactions: *Increased Heart Rate, Blood Pressure, and Ventricular Ectopic Activity*—A 10 to 20-mm increase in systolic blood pressure and an increase in heart rate of five to 15 beats per minute have been noted in most patients. (See Warnings regarding exaggerated chronotropic and pressor effects.) Approximately 5 percent of patients have had increased premature ventricular beats during infusions. These effects are dose related.

Miscellaneous Uncommon Effects—The following adverse effects have been reported in 1 to 3 percent of patients: nausea, headache, anginal pain, nonspecific chest pain, palpitations, and shortness of breath.

No abnormal laboratory values attributable to Dobutrex have been observed.

Longer-Term Safety—Infusions of up to 72 hours have revealed no adverse effects other than those seen with shorter infusions.

Overdosage: In case of overdosage, as evidenced by excessive alteration of blood pressure or by tachycardia, reduce the rate of administration or temporarily discontinue Dobutrex until the patient's condition stabilizes. Because the duration of action of Dobutrex is short, usually no additional remedial measures are necessary.

Administration and Dosage: *Reconstitution and Stability*—Dobutrex® (dobutamine hydrochloride, Lilly) is incompatible with alkaline solutions and should not be mixed with products such as 5% Sodium Bicarbonate Injection.

Dobutrex may be reconstituted with Sterile Water for Injection or 5% Dextrose Injection. To reconstitute, add 10 ml of diluent to Vial No. 7051 Dobutrex, 250 mg. If the material is not completely dissolved, add an additional 10 ml of diluent. The reconstituted solution may be stored under refrigeration for 48 hours or at room temperature for six hours.

Reconstituted Dobutrex must be further diluted to at least 50 ml prior to administration in 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Sodium Lactate Injection. Intravenous solutions should be used within 24 hours.

Solutions containing Dobutrex may exhibit a color that, if present, will increase with time. This color change is due to slight oxidation of the drug, but there is no significant loss of potency during the reconstituted time periods stated above.

Recommended Dosage—The rate of infusion needed to increase cardiac output usually ranges from 2.5 to 10 mcg/kg/min (see table). On rare occasions, infusion rates up to 40 mcg/kg/min have been required to obtain the desired effect.

Rates of Infusion for Concentrations of 250, 500, and 1000 mcg/ml

Drug Delivery Rate (mcg/kg/min)	Infusion Delivery Rate 250 mcg/ml* (ml/kg/min)	500 mcg/ml† (ml/kg/min)	1000 mcg/ml‡ (ml/kg/min)
2.5	0.01	0.005	0.0025
5	0.02	0.01	0.005
7.5	0.03	0.015	0.0075
10	0.04	0.02	0.01
12.5	0.05	0.025	0.0125
15	0.06	0.03	0.015

*250 mg per liter of diluent
†500 mg per liter or 250 mg per 500 ml of diluent
‡1000 mg per liter or 250 mg per 250 ml of diluent

The rate of administration and the duration of therapy should be adjusted according to the patient's response, as determined by heart rate, presence of ectopic activity, blood pressure, urine flow, and, whenever possible, measurement of central venous or pulmonary wedge pressure and cardiac output.

Concentrations up to 5000 mcg/ml have been administered to humans (250 mg/5 ml). The final volume administered should be determined by the fluid requirements of the patient. [08167

Lilly

Additional information available to the profession on request.

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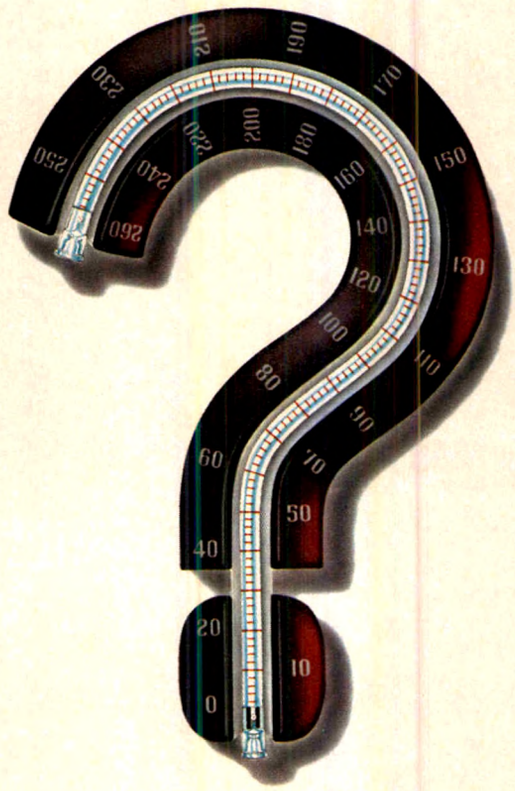
ANSWERS ABOUT ALDOMET®
(METHYLDOPA | MSD)

TO SOME IMPORTANT QUESTIONS ABOUT ANTIHYPERTENSIVE THERAPY.



For a brief summary of prescribing information, please see last page of this advertisement.

MSD
MERCK SHARP & DOHME

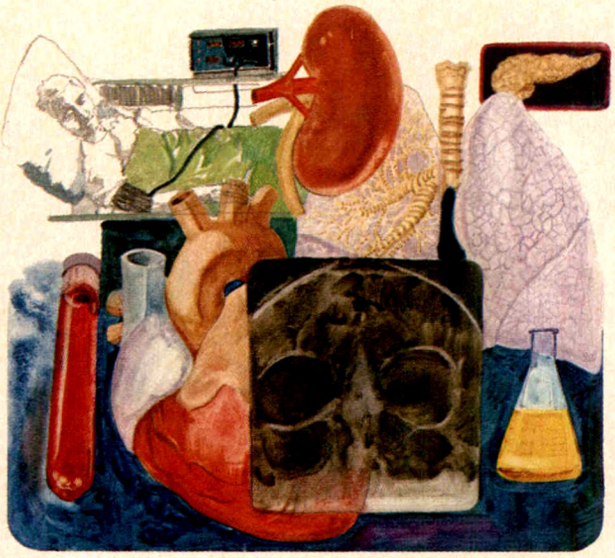
A109

IN ANTIHYPERTENSIVE THERAPY

...ANSWERS ABOUT

Can an antihypertensive be used in the vast majority of hypertensive patients, including certain patients requiring special considerations?

ALDOMET® CAN
(METHYLDOPA | MSD)



ALDOMET can be used in a wide range of hypertensives, including those with:

- ventricular hypertrophy
- hyperglycemia
- diabetes mellitus
- bronchial asthma
- allergic rhinitis
- hyperuricemia
- gouty arthritis
- sulfonamide hypersensitivity

ALDOMET (Methyldopa, MSD) is contraindicated in active hepatic disease, hypersensitivity to the drug, and if previous methyldopa therapy has been associated with liver disorders.

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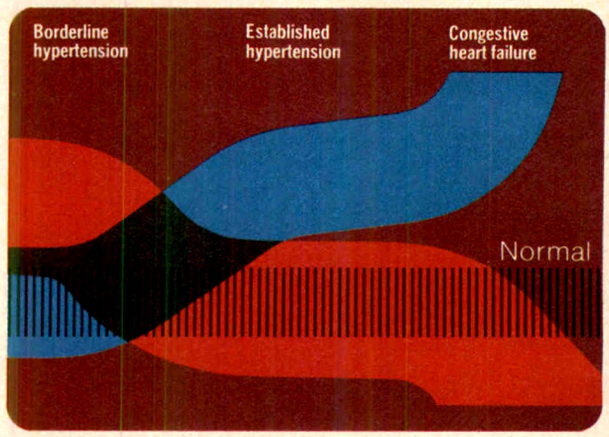
Does an antihypertensive lower blood pressure usually without lowering cardiac output?

ALDOMET DOES
(METHYLDOPA | MSD)

ALDOMET has no direct effect on cardiac function and lowers blood pressure usually without reducing cardiac output. Rather, it appears to reduce peripheral vascular resistance, the most commonly identified hemodynamic variable in hypertension (as hypertension progresses cardiac output tends to decrease and peripheral resistance tends to increase).

Hemodynamic Changes as Hypertension Progresses*



*adapted from Messerli and de Carvalho[1]

This may be particularly important in hypertensives with impaired cardiac function such as those with congestive heart failure*

*Edema may occur with ALDOMET. This is usually relieved by the use of a diuretic, but if edema progresses methyldopa should be discontinued.

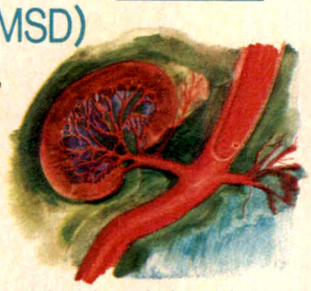
TABLETS: 500 mg, 250 mg, and 125 mg

ALDOMET® (METHYLDOPA | MSD)

The most prescribed nondiuretic antihypertensive in the U.S. today

Can an antihypertensive be effective usually without further reducing renal blood flow?

ALDOMET CAN (METHYLDOPA | MSD)



Glomerular filtration rate, filtration fraction, and renal blood flow are usually not reduced; therefore, ALDOMET is appropriate for many hypertensive patients with significantly impaired renal function. Since the drug is largely excreted by the kidney, patients with impaired renal function may respond to smaller doses.

Will an antihypertensive generally allow a normal cardiovascular response to exercise?

ALDOMET WILL (METHYLDOPA | MSD)

Cardiac output and blood pressure normally increase as the physical activities of the patient increase. ALDOMET does not significantly impair normal fluctuations of blood pressure during exercise.[2,3] This can be of importance to active hypertensive patients—such as athletic individuals or persons whose work requires substantial physical effort. With ALDOMET, exercise hypotension rarely occurs.

Sedation, usually transient, may occur during the initial period of therapy or whenever the dose is increased. Headache, asthenia, or weakness may be noted as early and transient symptoms.

Has an antihypertensive shown a proven record in long-term therapy?

ALDOMET HAS (METHYLDOPA | MSD)

A recent study[4] followed a group of patients on ALDOMET for ten years or more. The results suggest that ALDOMET is a highly effective medication for the long-term management of hypertension.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed.

1. Messerli FH, de Carvalho JGR: Management of mild hypertension. *Drug Therapy* 9:63-70, 1979.
2. Yasky J, Carosella C, Costa O: Diagnosis of arterial hypertension by means of graduated ergometric test, in Zanchetti, A (ed): *ALDOMET® (Methyldopa/MSD) in Worldwide Clinical Experience*, West Point, Pa, Merck Sharp & Dohme, 1979, pp 56-63.
3. Mancia G, Ferrari A, Gregorini G, et al: Effects of treatment with methyldopa on basal hemodynamics and on neural circulatory control, in Zanchetti, A (ed): *ALDOMET® (Methyldopa/MSD) in Worldwide Clinical Experience*, West Point, Pa, Merck Sharp & Dohme, 1979, pp 27-39.
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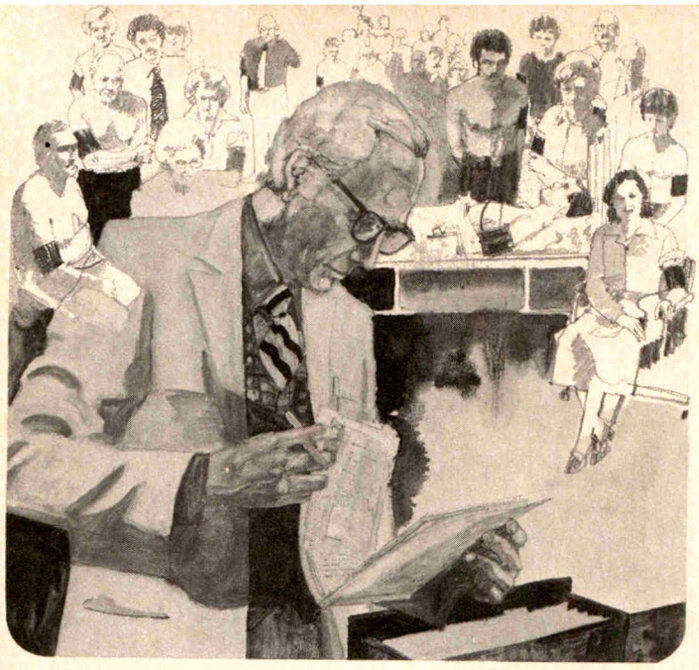
For a brief summary of prescribing information, please see following page.



ALDOMET®
(METHYLDOPA | MSD)

The most prescribed nondiuretic antihypertensive in the U.S. today

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, occasionally with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant or intend to nurse requires that anticipated benefits be weighed against possible risks; possibility of fetal injury or injury to a nursing infant cannot be excluded. Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression.

Cardiovascular: Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.)

Gastrointestinal: Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis.

Hepatic: Abnormal liver function tests, jaundice, liver disorders.

Hematologic: Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells, and rheumatoid factor.

Allergic: Drug-related fever, lupus-like syndrome, myocarditis.

Other: Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third months of therapy; increased dosage or adding a diuretic frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets, containing 125 mg methyldopa each, in bottles of 100; Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000; Tablets, containing 500 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 500.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

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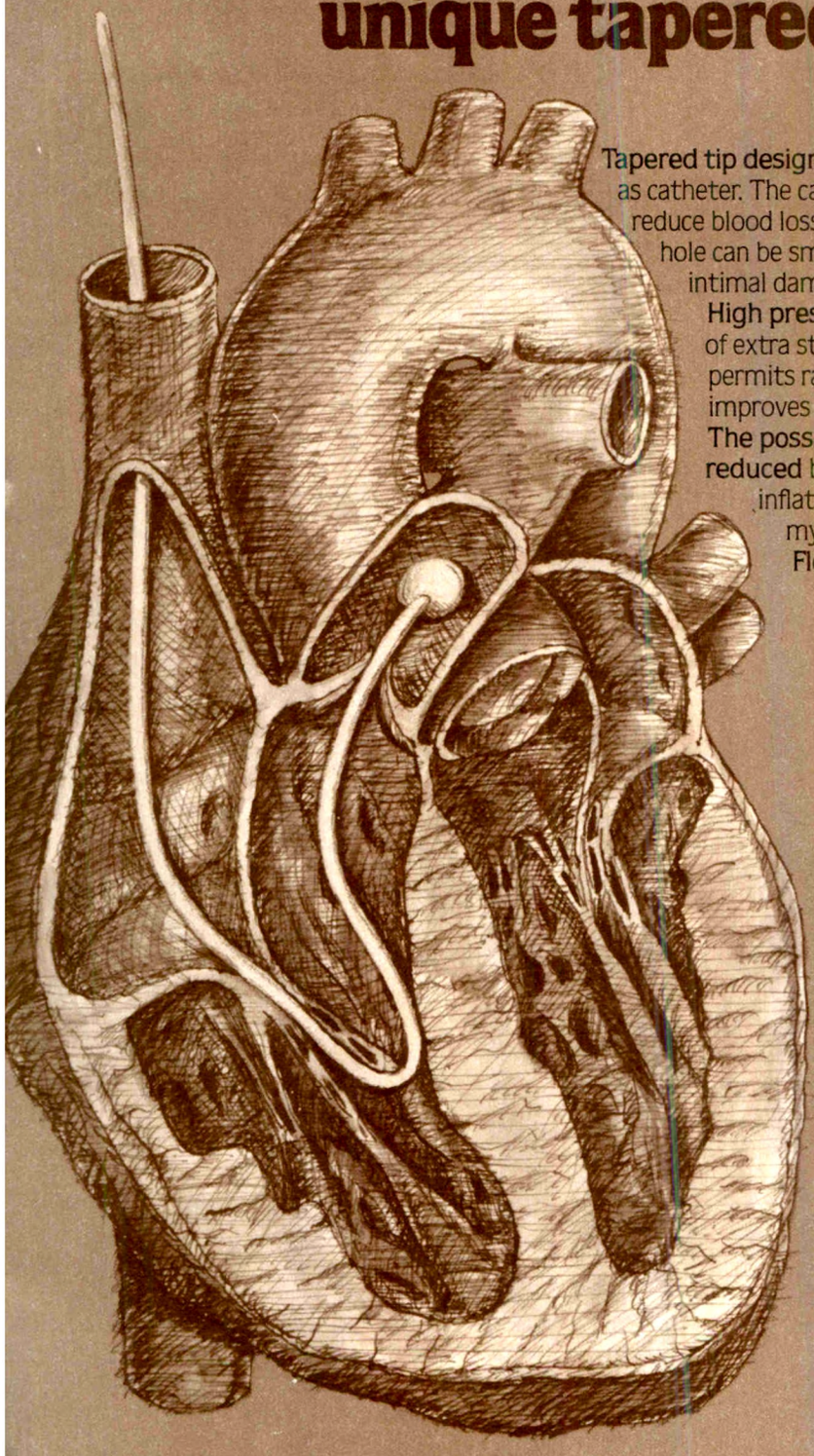

Tapered tip designed to permit use of same size introducer* as catheter. The catheter fits snugly in the introducer to reduce blood loss through the introducer. And the insertion hole can be smaller to give less likelihood of trauma and intimal damage.

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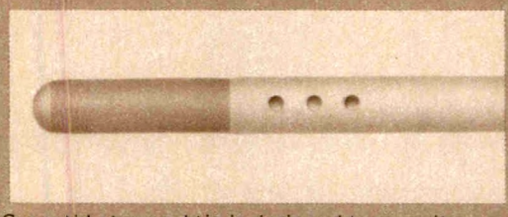
*Except 4F where balloon is 4½F.



Smoothly tapered tip is designed to permit use of the same size introducer as catheter.

extracorporeal

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Brief Summary of Product Information
BERMAN ANGIOGRAPHIC CATHETER

Indications: The Berman Angiographic Balloon Catheter is indicated for use in right-heart catheterization for cardiac angiography, pulmonary angiography, and measurement of the right-heart and pulmonary artery pressures. It can be used to inject radiopaque media and measure pressures in any chambers and vessels that can be entered from the right heart. **Contraindications:** This device is not designed, sold, or intended for use except as indicated. **Warnings:** Carbon dioxide MUST be used to inflate the balloon if there is a possibility that balloon rupture would result in air embolism in the left heart or systemic circulation. Do not inflate the latex balloon beyond the stated maximum inflation capacity. Angiograms should be done with the balloon inflated. When injecting radiopaque media, do not exceed the maximum flow rate and pressure for each Catheter. Transient obstruction of the pulmonary outflow tract, balloon rupture without serious sequelae, premature ventricular contractions, and knotting of the catheter have been reported as complications of the use of balloon catheters in cardiac diagnosis and monitoring. In addition, cardiac perforation and myocardial staining are known complications of pediatric catheterization. Care should be exercised when passing the Catheter in patients with left bundle-branch block. **Precautions:** Liquids must not be used as balloon-inflation media. Continuous electrocardiographic monitoring and continuous monitoring of the pressure at the side holes of the Catheter should be used during passage of the Catheter through the heart. The Catheter must be passed with fluoroscopic guidance to facilitate its manipulation into the appropriate chambers and vessels. The Catheter should be manipulated carefully and gently. Deflate the balloon prior to withdrawing the Catheter to avoid possible valve damage. Use aseptic technique throughout the procedure. The Berman Angiographic Balloon Catheter is intended for a SINGLE USE ONLY. DO NOT RESTERILIZE OR REUSE. Federal law (U.S.A.) restricts this device to sale by or on the order of a physician.

For complete instructions for use, see package insert.

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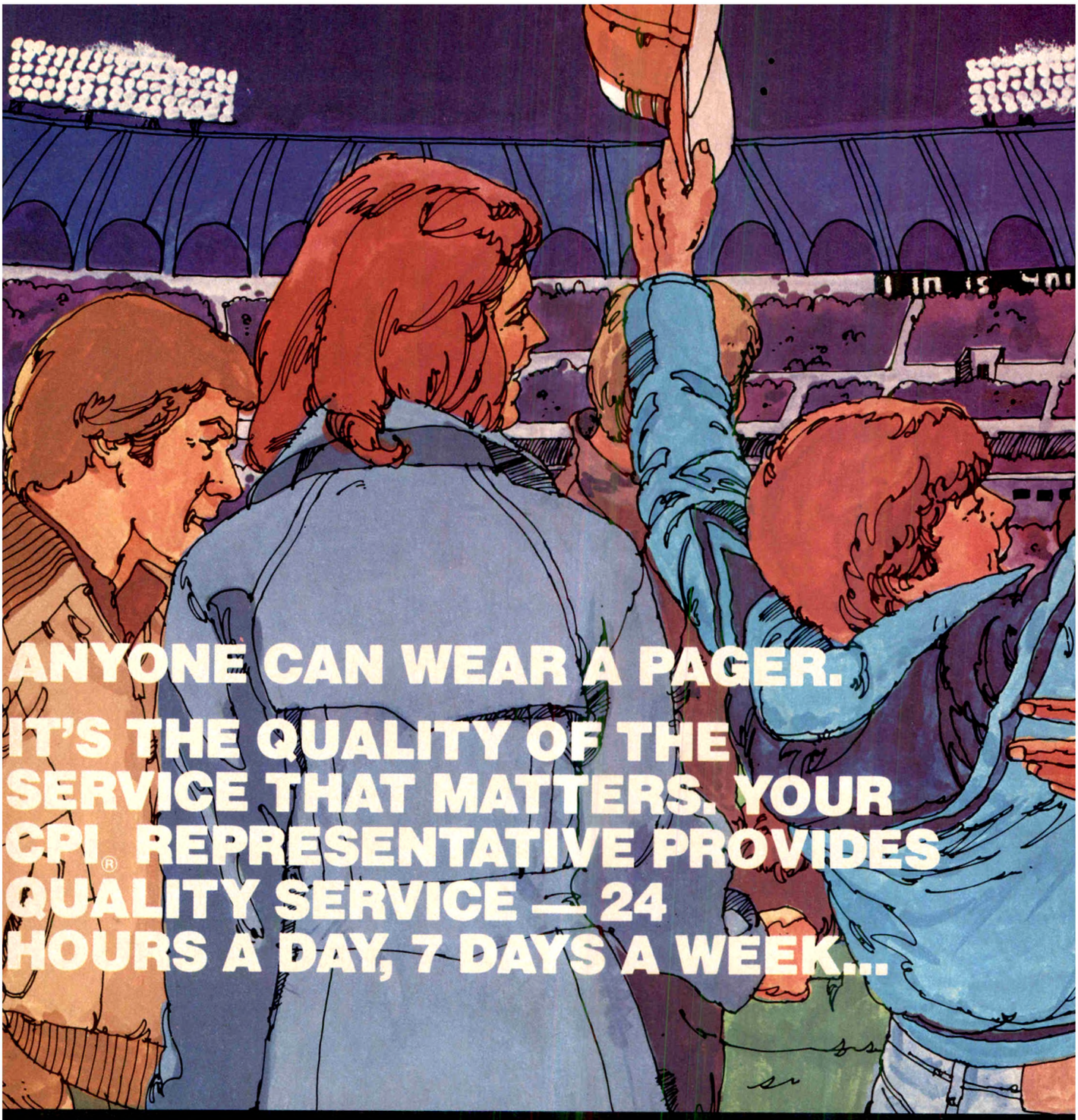

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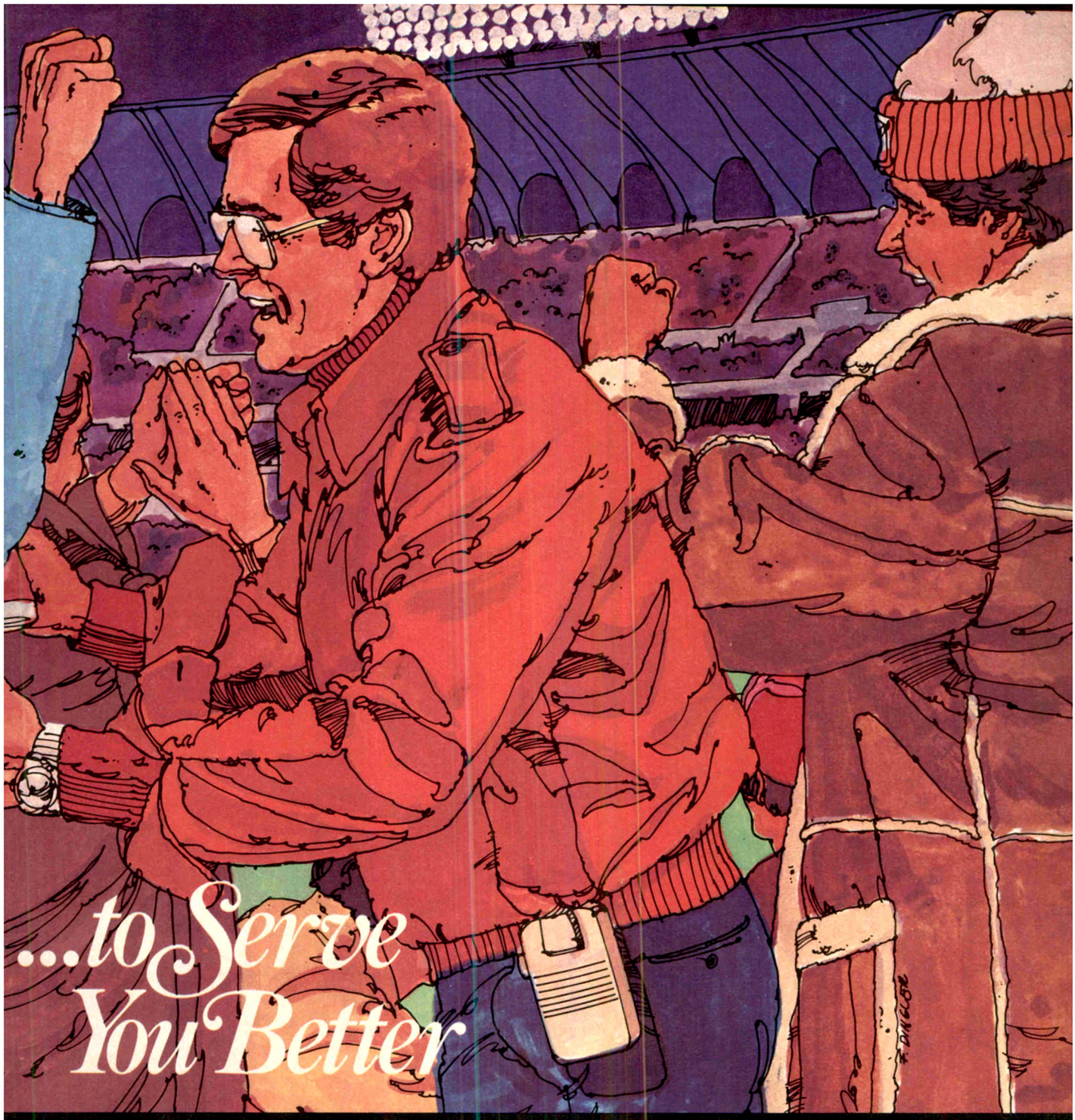

in a clinical setting or as representatives in the medical products industry. What this means to the physician is that CPI provides sales representatives with proven dedication to the health care industry.

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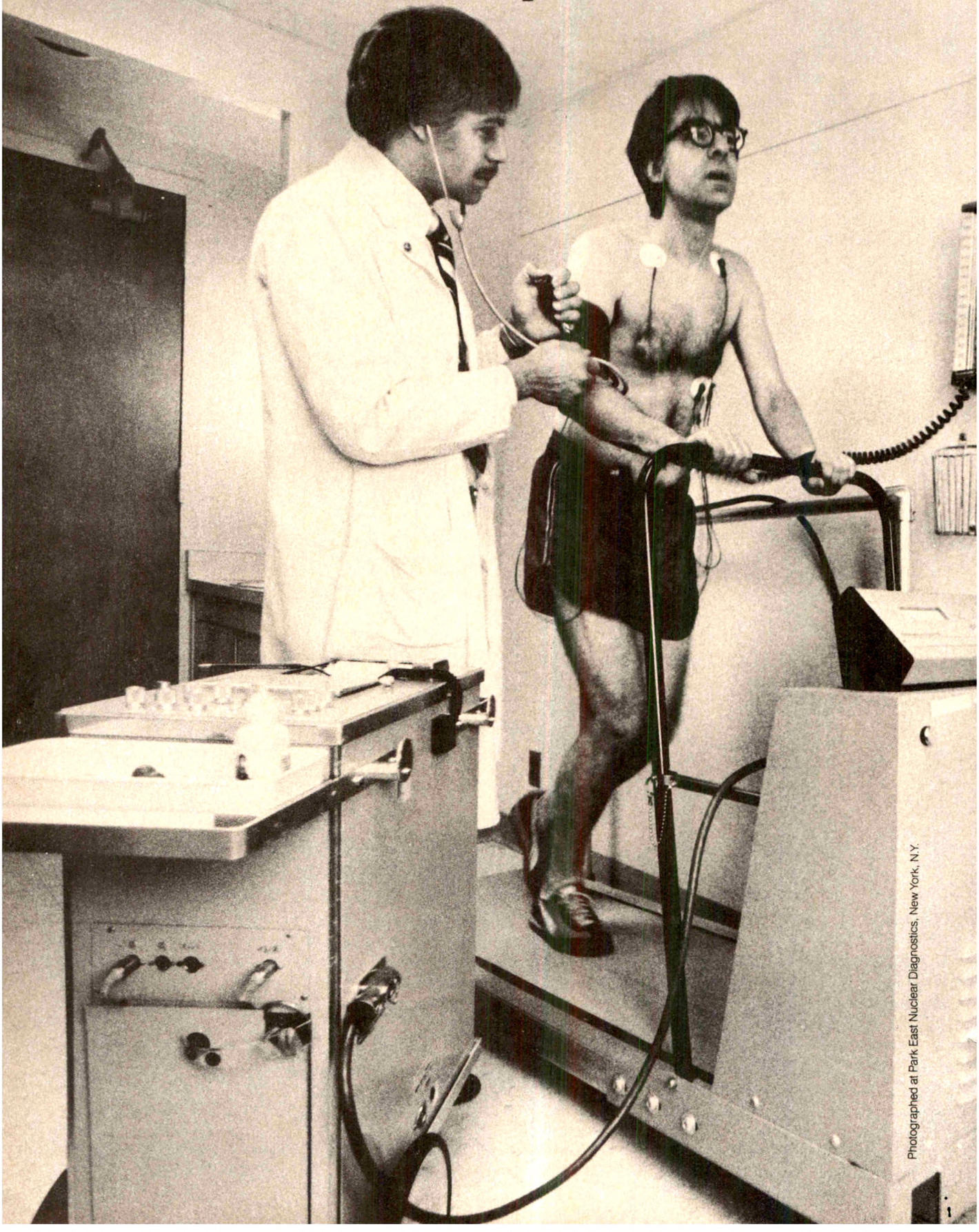
He denies symptoms of ischemic disease, but his stress ECG is positive.



Photographed at Park East Nuclear Diagnostics, New York, N.Y.

The stress ECG, once restricted to evaluation of symptomatic patients with suspected myocardial ischemia, has seen recent application in screening selected high-risk *asymptomatic* patients... airline flight crews, executives applying for corporate insurance policies and physical conditioning programs, security officials, and others.

However, 30% of asymptomatic patients with angiographically documented absence of significant coronary artery disease have false-positive stress tests.[1,2] Positive ECGs in such asymptomatic patients present a clinical management challenge: How much significance should be attributed to these findings? Although angiography can confirm absence of significant disease, many clinicians may hesitate to perform such an invasive procedure on asymptomatic patients in order to differentiate false from true positives.

Noninvasive thallium-201 imaging performed as an adjunct to the stress ECG can significantly enhance the specificity and sensitivity of electrocardiographic studies. Intravenously injected thallium-201 is taken up like potassium and concentrated most avidly by normal, well-perfused myocardial cells. Ischemic myocardial cells take up less thallium-201 – in proportion to the decrease in blood flow – particularly during maximal stress, when the differential in perfusion is most marked between regions supplied by normal coronary arteries and those supplied by stenotic vessels. Routinely available nuclear medicine imaging equipment can record any regional differences in thallium-201 uptake – and thus in myocardial perfusion – confirming the presence or absence of coronary disease.

Thallium imaging in conjunction with stress electrocardiography has proved to be a highly sensitive means of detecting CAD. In asymptomatic patients with a positive stress ECG, the specificity has approached 100%.[3]

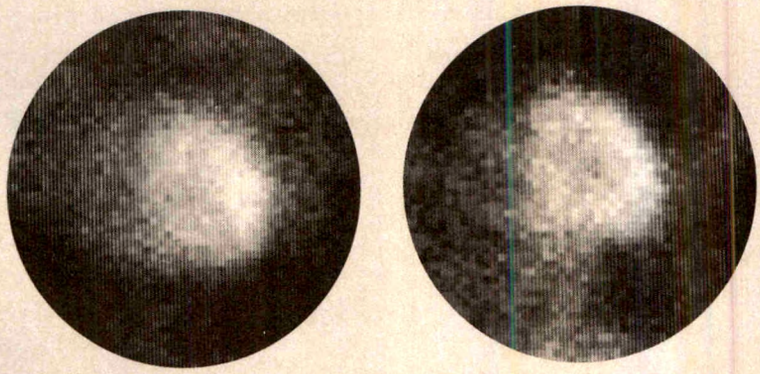
When an asymptomatic patient in your practice presents with positive stress ECG findings – consider a repeat stress study with thallium-201. Both research results and clinical experience have demonstrated that the combination of thallium-201 cardiography and the stress ECG can

- detect single-vessel disease in advance of electrocardiographic evidence[4]
- increase the sensitivity and specificity of the stress ECG, particularly in patients where ECG findings and symptomatology do not agree[5,6,7]
- identify those patients with clinically significant but electrically silent coronary disease – patients who will clearly need angiographic evaluation[7]

Unlike angiography, which displays the static anatomic details of the major coronary vessels, thallium imaging directly demonstrates – in a dynamic manner – the response of regional myocardial blood flow to coronary stenosis. Redistribution of thallium occurs over time into viable myocardium, representing stress-induced reversible ischemia, but not into regions of previous scar formation. Thus, initial perfusion defects that "fill in" on later images represent regions of viable myocardium that may benefit from medical or surgical control.

For asymptomatic patients with a positive stress ECG, the findings of a stress thallium-201 myocardial perfusion study may either rule out significant coronary stenosis, or provide a sound clinical basis for more invasive diagnostic evaluation.[6]

1. Bartel AG et al: Graded exercise stress test in angiographically documented coronary artery disease. *Circulation* **49**:348, 1974.
2. Goldschlager N et al: Treadmill stress tests as indicators of presence and severity of coronary artery disease. *Ann Intern Med* **85**:277, 1976.
3. Berman DS et al: Exercise myocardial scintigraphy with thallium-201: Evaluation of asymptomatic patients with positive treadmill electrocardiograms. Proceedings of the Western Regional Society of Nuclear Medicine Meeting, Las Vegas, October 1977.
4. Bailey IK et al: Thallium-201 myocardial perfusion imaging at rest and during exercise. Comparative sensitivity to electrocardiography in coronary artery disease. *Circulation* **55**:79, 1977.
5. Blood DK et al: Comparison of thallium-201 myocardial scans at rest with scans four hours after exercise. *Circulation* **56** (suppl 3): 229, 1977.
6. Raphael LD et al: Thallium exercise myocardial scintigraphy in patients with "angina and normal coronary arteriograms" (abs). *Circulation* **53-54** (suppl 2): 217, 1976.
7. Ritchie JL et al: Myocardial imaging with thallium-201 at rest and during exercise. Comparison with coronary arteriography and resting and stress electrocardiography. *Circulation* **56**:66, 1977.



Anterior thallium studies of 45-year-old male with positive exercise ECG but no symptoms of stress-induced ischemia. Postexercise image (left) reveals inferior-wall perfusion deficit. Image made 4 hours later (right) demonstrates reperfusion, confirms presence of coronary disease.

Thallous Chloride Tl 201

NEN New England Nuclear®

Please see following page for brief prescribing information.

Thallous Chloride Tl 201

For Diagnostic Use

November 1977

Indications and Usage: Thallous Chloride Tl 201 may be useful in myocardial perfusion imaging for the diagnosis and localization of myocardial infarction.

It may also be useful in conjunction with exercise stress testing as an adjunct in the diagnosis of ischemic heart disease (atherosclerotic coronary artery disease).

Contraindications: None known.

Warnings: In studying patients in whom myocardial infarction or ischemia is known or suspected, care should be taken to assure continuous clinical monitoring and treatment in accordance with safe, accepted procedure. Exercise stress testing should be performed only under the supervision of a qualified physician and in a laboratory equipped with appropriate resuscitation and support apparatus.

Ideally, examinations using radiopharmaceutical drug products—especially those elective in nature—of women of childbearing capability should be performed during the first ten days following the onset of menses.

Precautions: Data are not available concerning the effect of marked alterations in blood glucose, insulin, or pH (such as is found in diabetes mellitus) on the quality of thallium Tl 201 scans. Attention is directed to the fact that thallium is a potassium analog, and since the transport of potassium is affected by these factors, the possibility exists that the thallium may likewise be affected.

Thallous Chloride Tl 201, as all radioactive materials, must be handled with care and used with appropriate safety measures to minimize external radiation exposure to clinical personnel. Care should also be taken to minimize radiation exposure to patients in a manner consistent with proper patient management.

No long-term animal studies have been performed to evaluate carcinogenic potential.

Adequate reproduction studies have not been performed in animals to determine whether this drug affects fertility in males or females, has teratogenic potential, or has other adverse effects on the fetus. Thallous Chloride Tl 201 should be used in pregnant women only when clearly needed.

It is not known whether this drug is excreted in human milk. As a general rule nursing should not be undertaken when a patient is administered radioactive material.

Safety and effectiveness in children have not been established.

Adverse Reactions: Adverse reactions related to use of this agent have not been reported to date.

Dosage and Administration: The recommended adult (70kg) dose of Thallous Chloride Tl 201 is 1-1.5mCi. Thallous Chloride Tl 201 is intended for intravenous administration only.

For patients undergoing resting thallium studies, imaging is optimally begun within 10-20 minutes after injection. Several investigators have reported improved myocardial-to-background ratios when patients are injected in the fasting state, in an upright posture, or after briefly ambulating.

Best results with thallium imaging performed in conjunction with exercise stress testing appear to be obtained if the thallium is administered when the patient reaches maximum stress and when the stress is continued for 30 seconds to one minute after injection. Imaging should begin within ten minutes post-injection since target-to-background ratio is optimum by that time. Several investigators have reported significant decreases in the target-to-background ratios of lesions attributable to transient ischemia by two hours after the completion of stress testing.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

Radiopharmaceuticals should be used by persons with specific training in the safe use and handling of radionuclides produced by nuclear reactor or particle accelerator and whose experience and training have been approved by the appropriate government agencies authorized to license the use of radionuclides.

How Supplied: Thallous Chloride Tl 201 for intravenous administration is supplied as a sterile, non-pyrogenic solution containing at calibration time, 1mCi/ml of Thallous Tl 201, 9mg/ml sodium chloride, and 9mg/ml of benzyl alcohol. The pH is adjusted to between 4.5-6.5 with hydrochloric acid and/or sodium hydroxide solution. Vials are available in the following quantities of radioactivity: 1.5, 3.0, 4.5, 6.0, and 9.0 millicuries of Thallous Tl 201.

The contents of the vial are radioactive. Adequate shielding and handling precautions must be maintained.

Catalog Number NRP-427

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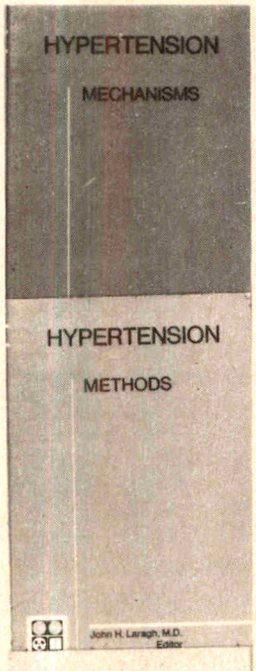

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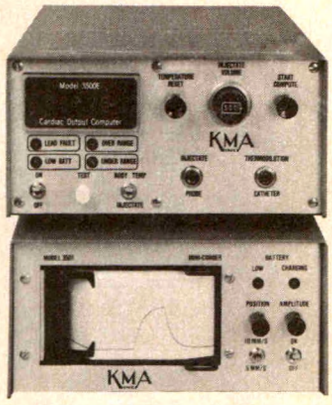

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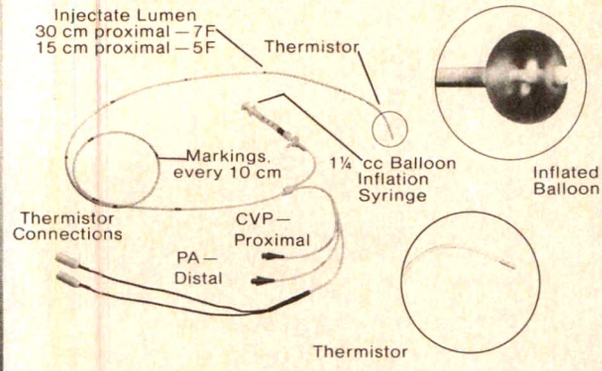

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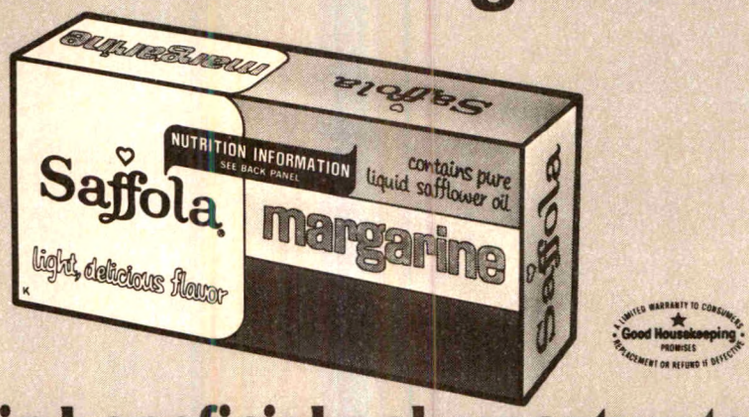

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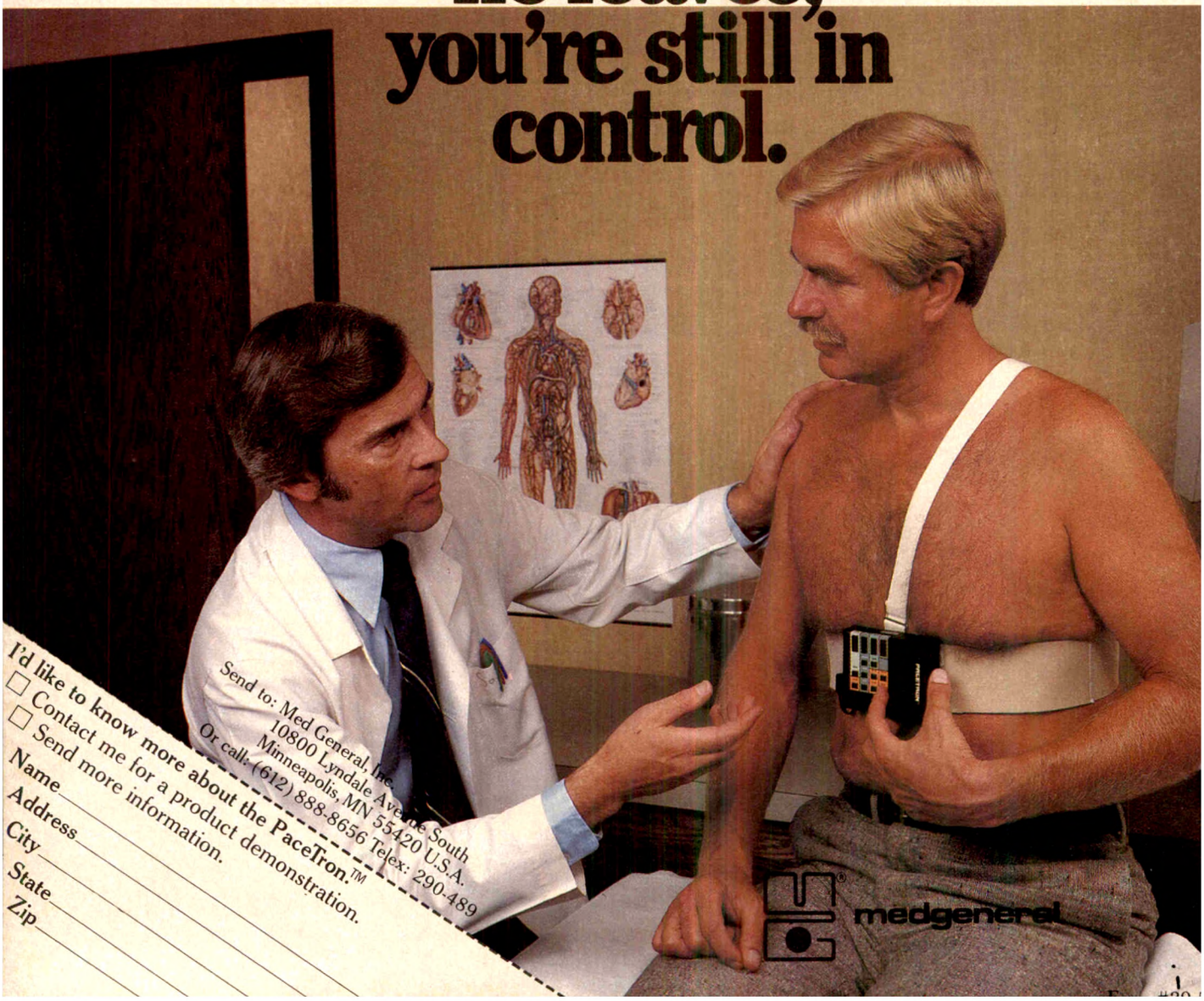

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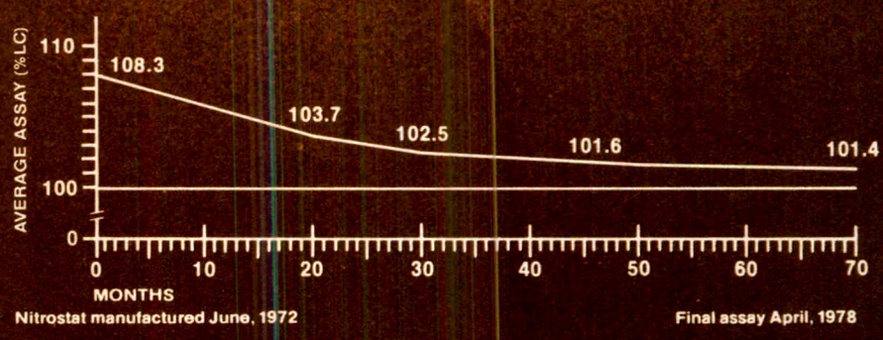

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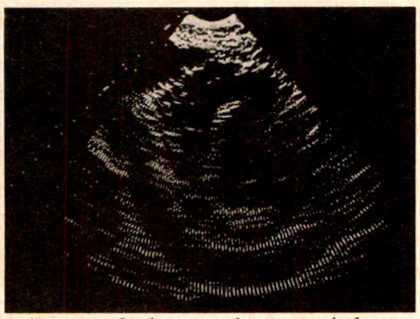
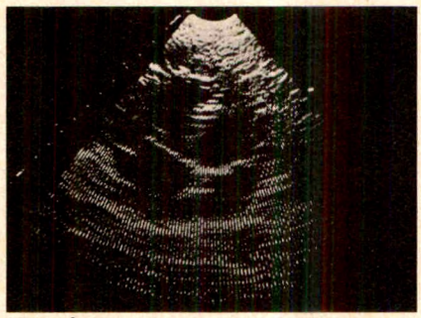


Left ventricular hypertrophy, pericardial effusion.



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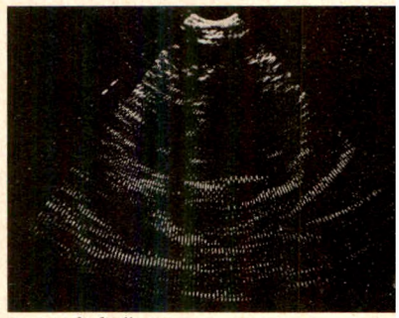
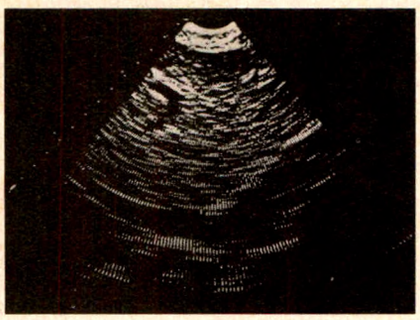
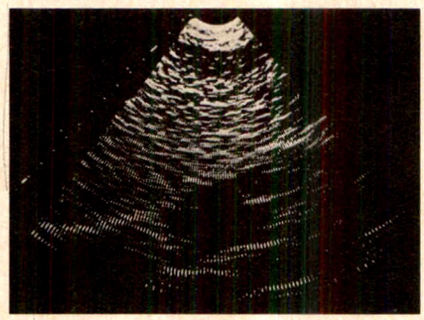


Pericardial effusion.



Inferior Vena Cava entering right atrium.



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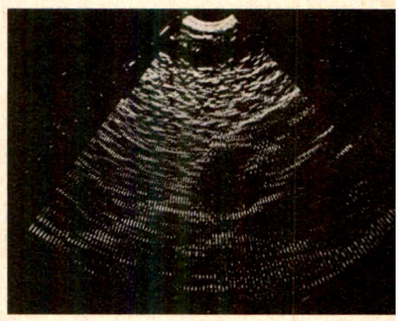
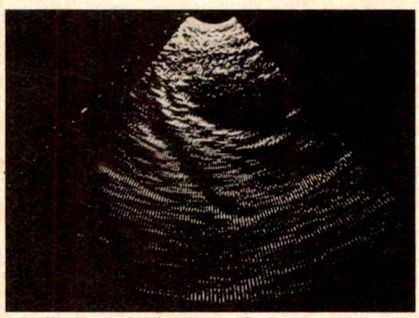
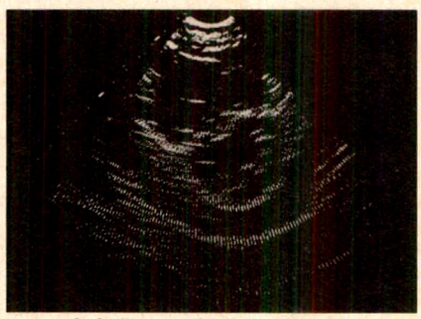


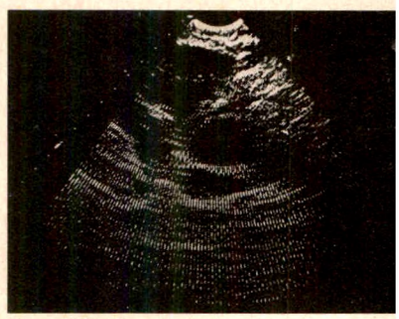
Tricuspid valve vegetation.



Small pericardial effusion, long axis view.



Pericardial effusion, short axis view.



Tricuspid valve vegetation.

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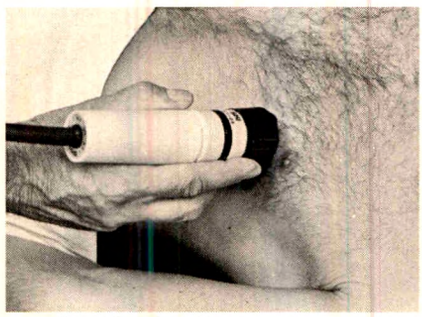

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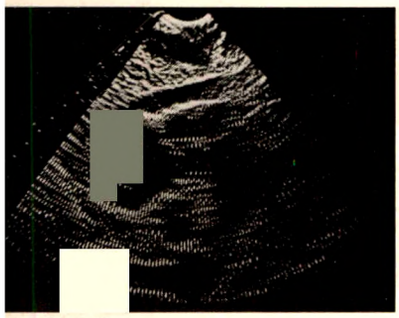
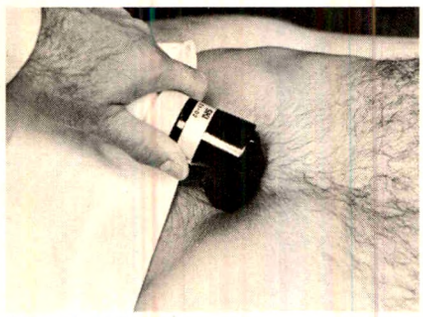
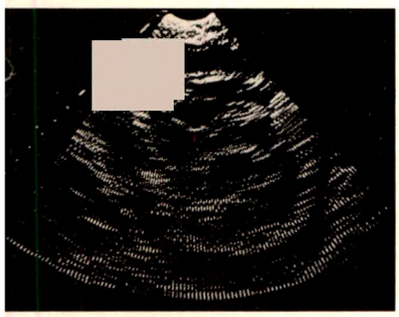


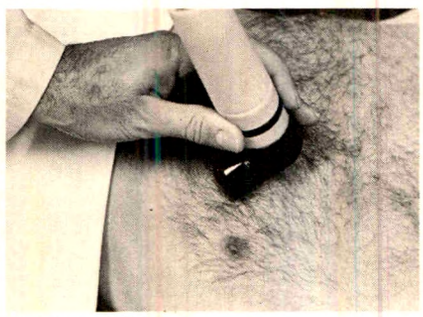
ricardial effusion.



Subxyphoid Views



ft ventricular hypertrophy pericardial usion, short axis.



Parasternal Views

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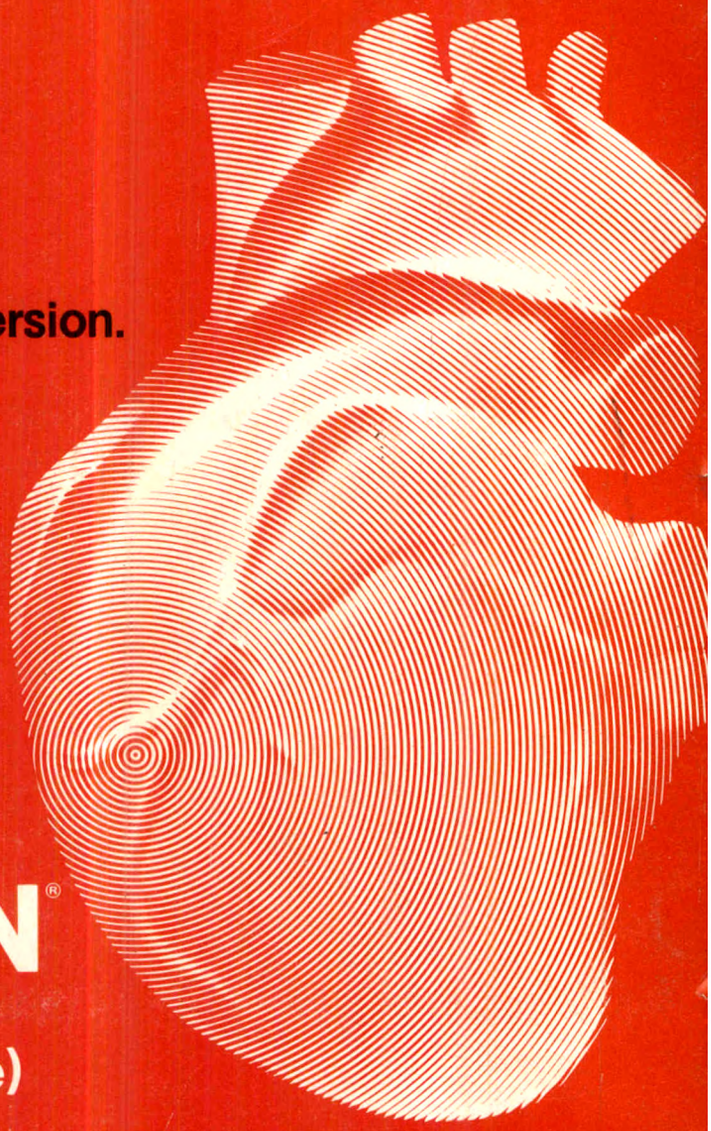

For ventricular arrhythmias.
For atrial arrhythmias.
For smooth, trouble-free conversion.
For steady maintenance.

CARDIOQUIN®
TABLETS
(quinidine polygalacturonate)

- ☐ Greater GI tolerance than with quinidine sulfate
- ☐ Full quinidine cardiodynamics
- ☐ Convenient b.i.d. or t.i.d. dosage for most patients

CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of a broad range of cardiac arrhythmias (see Brief Summary). After conversion to normal sinus rhythm —whether with CARDIOQUIN Tablets or electroconversion— only low b.i.d. or t.i.d. dosage of this unique polygalacturonate salt of quinidine is required for maintenance in most cases. The polygalacturonic acid serves as a buffering moiety. It protects the mucosa of the stomach and permits dependable absorption of the quinidine.*

*Aviado, D. M., Krantz and Carr's Pharmacologic Principles of Medical Practice, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heart-block; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 100.

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OCTOBER 22, 1979

The American Journal of CARDIOLOGY®

OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

Symposium on Nifedipine and Calcium Flux Inhibition in the Treatment of Coronary Arterial Spasm and Myocardial Ischemia

Bernard Lown, MD, FACC, Guest Editor

Symposium on the Heart in Hypertension

Robert C. Tarazi, MD, FACC, Guest Editor

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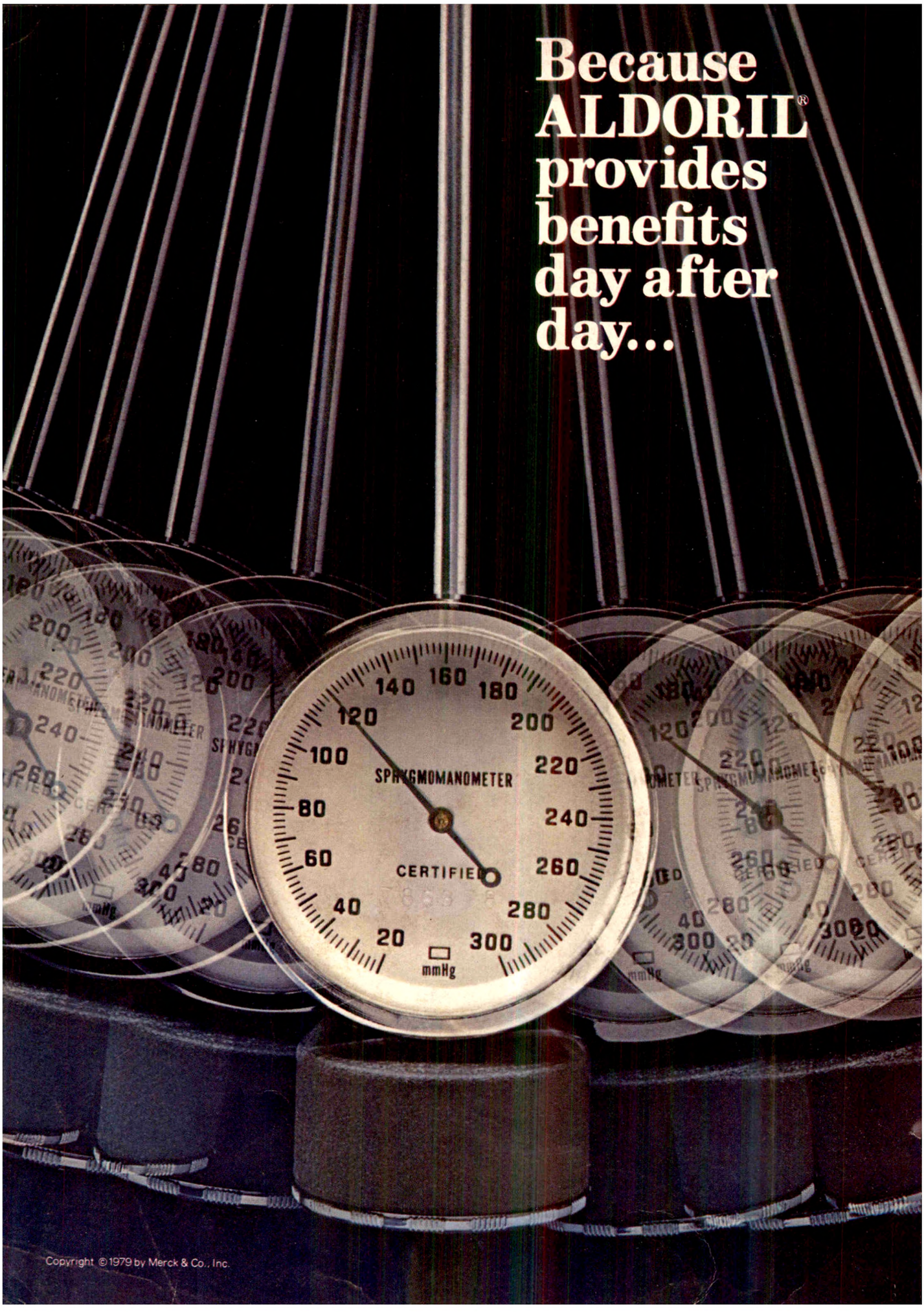
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many hypertensives have benefited year after year

cardiovascular benefits

- **cardiac output usually maintained**
- **sodium and fluid retention generally controlled**
- **two highly effective complementary agents**

As a fixed combination, ALDORIL is not indicated for initial therapy since hypertension requires therapy titrated to the individual patient. If an available strength of ALDORIL meets the patient's titrated needs, the combination drug may be more convenient in patient management. Therapy should be reevaluated as necessary.

ALDORIL is contraindicated in active hepatic disease; anuria; hypersensitivity to methyldopa or to hydrochlorothiazide or other sulfonamide-derived drugs; if previous methyldopa therapy has been associated with liver disorders. In patients with renal disease, thiazides may precipitate azotemia. Use with caution in patients with severe renal disease or impaired hepatic function.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details, see the brief summary of prescribing information.

For a brief summary of prescribing information, please see following page.

practical benefits

- **effects on daily activities usually minimal:** There is less frequent symptomatic postural hypotension with ALDORIL than with many other antihypertensive agents. Exercise hypotension and diurnal blood pressure variations rarely occur.
- **greater dosage convenience:** a b.i.d. regimen is possible for many patients
- **four dosage strengths:** offer the widest range of dosage strengths available in a combination antihypertensive

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ALDORIL® D50 containing 500 mg ALDOMET® (Methyldopa, MSD) and 50 mg HydroDIURIL® (Hydrochlorothiazide, MSD)

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containing methyldopa and hydrochlorothiazide

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methyldopa 500 mg and hydrochlorothiazide 50 mg

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methyldopa 500 mg and hydrochlorothiazide 30 mg

ALDORIL®-25
methyldopa 250 mg and hydrochlorothiazide 25 mg

ALDORIL®-15
methyldopa 250 mg and hydrochlorothiazide 15 mg

WARNING

This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see **Warnings**); anuria; routine use in an otherwise healthy pregnant woman with or without mild edema; hypersensitivity to methyldopa or to hydrochlorothiazide or other sulfonamide-derived drugs.

Warnings: METHYLDOPA—**It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.**

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within the first three weeks of therapy, sometimes with eosinophilia or abnormalities in one or more liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually within the first two to three months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever, abnormalities in liver function tests, or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, reversible reduction of white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Follow patients carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

HYDROCHLOROTHIAZIDE—Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects may develop in patients with impaired renal function. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. May add to or potentiate action of other antihypertensive drugs; potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity; read circulars for lithium preparations before use of such concomitant therapy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant requires that anticipated benefits be weighed against possible risks.

Methyldopa and thiazides cross the placental barrier and appear in cord blood.

No unusual adverse reactions have been reported in association with the use of methyldopa during pregnancy. Although no obvious teratogenic effects have been reported, the possibility of fetal injury cannot be excluded.

The hazards of thiazides crossing the placental barrier include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in adults. Methyldopa and thiazides appear in breast milk. Patients taking ALDORIL should not nurse.

Precautions: METHYLDOPA—Should be used with caution in patients with history of previous liver disease or dysfunction (see **Warnings**). May interfere with measurement of urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites. Involuntary choreoathetotic movements have been observed in patients with severe bilateral cerebrovascular disease. If such movements occur, stop the drug. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

HYDROCHLOROTHIAZIDE—Perform periodic determination of serum electrolytes to detect possible electrolyte imbalance. Observe all patients for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, in severe cirrhosis, with concomitant corticosteroids or ACTH, or with inadequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest. Thiazides may increase responsiveness to tubocurarine. Antihypertensive effects of the drug may be enhanced in postsympathectomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid glands with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged therapy; thiazides should be discontinued before testing for parathyroid function.

Adverse Reactions: METHYLDOPA—*Central nervous system:* Sedation, headache, asthenia or weakness; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression. *Cardiovascular:* Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.) *Gastrointestinal:* Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis. *Hepatic:* Abnormal liver function tests, jaundice, liver disorders. *Hematologic:* Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells and rheumatoid factor. *Allergic:* Drug-related fever, lupus-like syndrome, myocarditis. *Other:* Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

HYDROCHLOROTHIAZIDE—*Gastrointestinal system:* Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis. *Central nervous system:* Dizziness, vertigo, paresthesias, headache, xanthopsia. *Hematologic:* Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, hemolytic anemia. *Cardiovascular:* Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics). *Hypersensitivity:* Purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), fever, respiratory distress including pneumonitis, anaphylactic reactions. *Other:* Hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, transient blurred vision. Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

Note: Tolerance may occur, usually between the second and third month of therapy. Increasing dosage of either component separately or together frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

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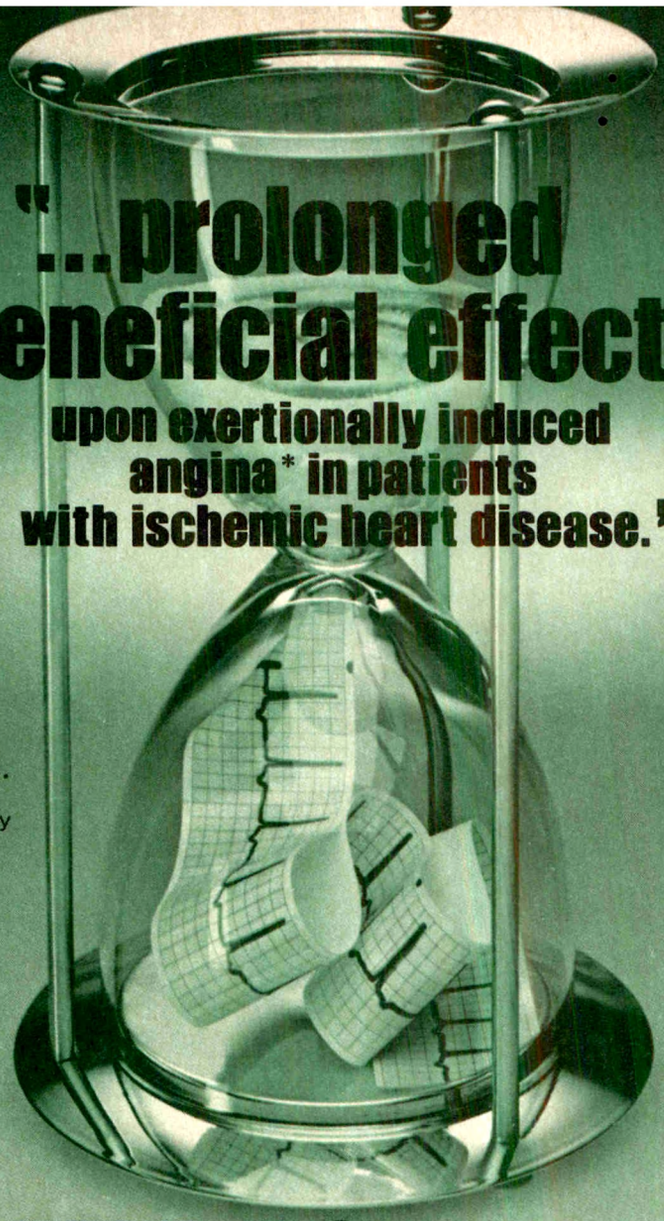

A double-blind, controlled study of 28 patients employing maximal treadmill exercise stress tests.

1. Antianginal efficacy of oral therapy with isosorbide dinitrate capsules. Lee G, Mason DT, Amsterdam EA, Miller RR, and DeMaria, AN. *Chest* 73:327-333, 1978.

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"Possibly" effective: When taken by the oral route, Isordil is indicated for the relief of angina pectoris (pain of coronary artery disease). It is not intended to abort the acute anginal episode, but is widely regarded as useful in the prophylactic treatment of angina pectoris.
Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.

Warnings: Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

Consult direction circular before prescribing.

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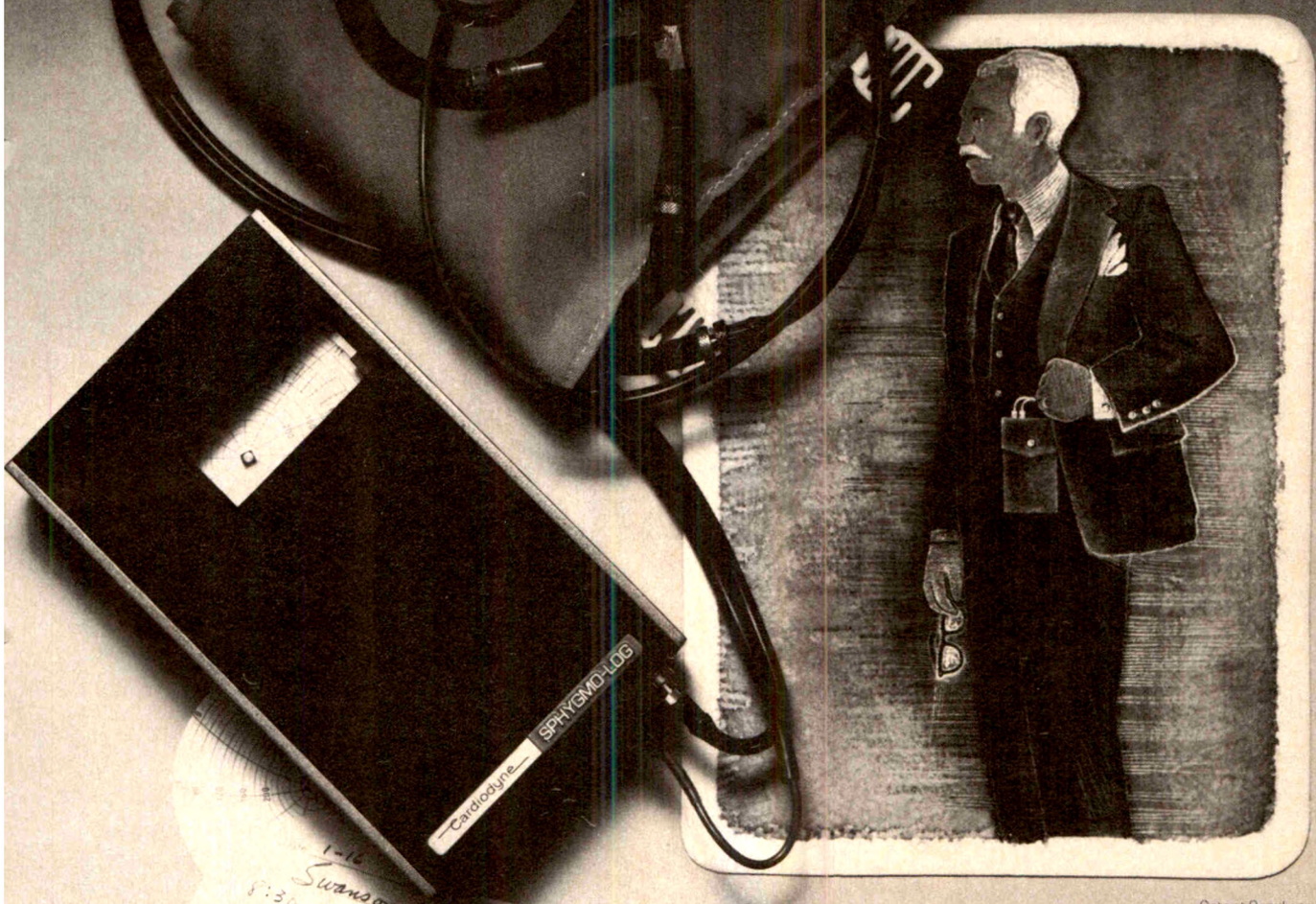

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1. *HEW News*, publication 79-6. U.S. Department of Health, Education, and Welfare (Food and Drug Administration), March 30, 1979, p. 1.

†Data on file and available upon request from Hoechst-Roussel Pharmaceuticals Inc., Somerville, N.J. 08876.

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INDICATIONS: Edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Hypertension when used alone or in combination with other antihypertensive drugs; patients not adequately controlled with thiazides also probably will not be adequately controlled with furosemide alone.

CONTRAINDICATIONS: Because animal reproductive studies have shown that furosemide may cause fetal abnormalities, the drug is contraindicated in women of childbearing potential. Anuria. History of hypersensitivity to the compound.

WARNINGS: Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Exercise care in patients receiving potassium-depleting steroids. Perform frequent serum electrolyte, CO_2, and BUN determinations during first few months of therapy and periodically thereafter, and correct abnormalities or temporarily withdraw the drug. Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital. Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Discontinue furosemide if increasing azotemia and oliguria occur during treatment of severe, progressive renal disease. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions. Furosemide may potentiate the therapeutic effect of other antihypertensive agents. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Exacerbation or activation of systemic lupus erythematosus may occur. Furosemide appears in breast milk. If use of the drug is essential, the patient should stop nursing. Cases of tinnitus and reversible hearing impairment have been reported.

There have also been some reports of cases in which irreversible hearing impairment occurred. Usually ototoxicity has been reported when furosemide was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were given. If the physician elects to use high-dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, an infusion rate not exceeding 4 mg furosemide per minute has been used.)

PRECAUTIONS: As with any effective diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Patients receiving furosemide should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with furosemide as with any other potent diuretic, especially with brisk diuresis, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis may exaggerate metabolic effects of hypokalemia, especially with reference to myocardial activity. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Periodic serum calcium levels should be obtained. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Furosemide has a tendency to antagonize the effects of tubocurarine and may potentiate the action of succinylcholine. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Furosemide may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

It has been reported in the literature that coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of Lasix (furosemide) in some patients. This effect has been attributed to inhibition of prostaglandin synthesis by indomethacin. Indomethacin may also affect plasma renin levels and aldosterone excretion: this should be borne in mind when a renin profile is evaluated in hypertensive patients. Patients receiving both indomethacin and Lasix (furosemide) should be observed closely to determine if the desired diuretic and/or antihypertensive effect of Lasix (furosemide) is achieved.

ADVERSE REACTIONS: Anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, blurred vision, tinnitus and hearing loss, anemia, leukopenia, agranulocytosis (rare), thrombocytopenia, aplastic anemia (rare), purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), exfoliative dermatitis, erythema multiforme, pruritus. Orthostatic hypotension may occur and may be exaggerated by alcohol, barbiturates, or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis.

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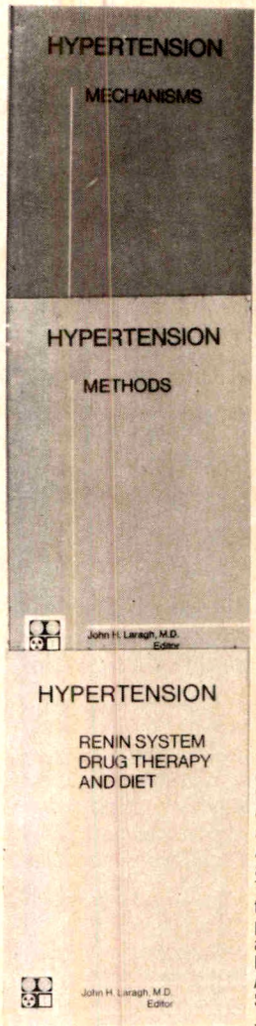

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VOLUME 44

NUMBER 5

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ROBERT S. ADELSTEIN and DAVID R. HATHAWAY

This review of the mechanism by which calcium and cyclic adenosine monophosphate (cyclic AMP) may regulate the interaction of smooth muscle actin and myosin indicates that calcium initiates smooth muscle contraction by activating the enzyme, myosin light chain kinase. This action requires (1) the binding of calcium to a 16,500 dalton calcium-finding protein (calmodulin), and (2) the binding of calmodulin-calcium to a 125,000 dalton catalytic subunit. Phosphorylation of mysoin light chain kinase decreases the activity of the enzyme, favoring the unphosphorylated form of myosin, which cannot interact with actin to produce smooth muscle contraction. Regulation of smooth muscle contraction phosphorylation does not preclude the existence of other regulatory mechanisms, which may also involve calcium.

788 **Significance of Spasm in the Pathogenesis of Ischemic Heart Disease**
ATTILIO MASERI, ANTONIO L'ABBATE, SERGIO CHIERCHIA, OBERDAN PARODI, SILVA SEVERI, ANDREA BIAGINI, ALESSANDRO DISTANTE, MARIO MARZILLI and ANNA MARIA BALLESTRA

Using continuous hemodynamic and electrocardiographic monitoring thallium-201 scintigraphy and coronary arteriography during ischemic attacks in patients with angina at rest or during exercise, or both, these investigators demonstrated a vasospatic origin for the attacks. They maintain myocardial ischemia can occur with little or no atherosclerosis and that it is essential to identify the causes of acute myocardial ischemia independent of the degree of coronary atherosclerosis or of increased myocardial oxygen demand. Vasospasm plays an important role in producing myocardial ischemia and even serious arrhythmias. They recommend for such patients in whom coronary arterial spasm is the main cause of myocardial ischemia, nitrates, which prevent excessive muscle contraction and reduce afterload, as well as calcium antagonists, which prevent smooth muscle contraction. They use intravenous infusions of nitrates and calcium nitrates and calcium antagonists in severely ill patients and taper dosages in less seriously ill patients or patients whose condition is improving.

793 **Inappropriate Coronary Vasoconstriction in Patients With Coronary Artery Disease: A Role for Nifedipine?**
STEPHEN GUNTHER, LAURENCE GREEN, JAMES E. MULLER, GILBERT H. MUDGE, Jr. and WILLIAM GROSSMAN

Not all angina pectoris results from an imbalance between a fixed, restricted myocardial oxygen supply and transiently increased metabolic demand. Measurements of coronary sinus vascular resistance by the thermodilution method demonstrate the presence of inappropriate coronary arterial vasoconstriction in patients with coronary artery disease during cold pressor testing. Therapy with the usual antianginal agents may not be effective in preventing myocardial ischemia produced by primary coronary vasoconstriction in patients with coronary artery disease. A potent vasodilator drug, like nifedipine, with specificity for the coronary circulation and little or no effect in clinical doses on systemic hemodynamics or myocardial contractility, appears ideal. Preliminary results indicate that nifedipine is clinically effective in blocking inappropriate coronary vasoconstriction in patients with typical angina and may prove a useful addition to the treatment of ischemic heart disease.

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*INDICATIONS—Based on a review of this drug by the National Academy of Science-National Research Council and/or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.

ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg (2 tablets) three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.
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798 Nifedipine Therapy for Refractory Coronary Arterial Spasm
FREDERICK A. HEUPLER, Jr. and WILLIAM L. PROUDFIT

Nifedipine given to eight patients with intractable coronary arterial spasm and Prinzmetal's variant angina decreased the frequency of their ischemic attacks with few minor side effects. Holter monitor evaluation confirmed the absence of ischemic changes while the patients were taking nifedipine. The average number of attacks of angina decreased from 104 a month before nifedipine therapy to 8 a month during therapy. One patient had recurrent ventricular tachycardia only during episodes of S-T segment elevation; the tachycardia was refractory to antiarrhythmic therapy and was controlled when nifedipine prevented the coronary spasm and S-T segment elevation.

804 Nifedipine in the Treatment of Prinzmetal's (Variant) Angina
SHELDON GOLDBERG, NATHANIEL REICHEK, JOHN WILSON, JOHN W. HIRSHFELD, Jr., JAMES MULLER and JOHN A. KASTOR

In this clinical study of 12 patients with variant angina pectoris the pain at rest disappeared within 24 hours in 11 subjects given optimal doses of nifedipine. Withdrawal of nifedipine led to recurrent angina on six occasions in four patients. In a follow-up period of 3 weeks to 11 months, 7 of the 11 patients who had shown improvement continued to have an exellent response and were asymptomatic or had only infrequent anginal attacks easily relieved with nitroglycerin. Provocative testing in the cardiac laboratory showed that nifedipine can block both alpha adrenergic- and ergonovine-induced vasospasm. Long-term side effects caused by the systemic vasodilatory action of the drug included headache, digital dysesthesias, leg cramps and flushing.

811 Nifedipine Therapy for Stable Angina Pectoris: Preliminary Results of Effects on Angina Frequency and Treadmill Exercise Response
RALPH M. MOSKOWITZ, PAUL A. PICCINI, GERALD V. NACARELLI and ROBERT ZELIS

In a single blind study nifedipine given for 2 weeks or longer, in 10 patients with stable angina pectoris secondary to atherosclerotic coronary artery disease decreased the frequency of anginal attacks and the comsumption of nitroglycerin and increased the duration of treadmill exercise. All patients had a documented history of previous transmural myocardial infarction or a coronary arteriogram showing 70 percent or greater narrowing of at least one major coronary artery. Side effects from nifedipine were minor and easily tolerable. These results suggest nifedipine prolongs exercise time by decreasing heart rate × systolic blood pressure product at a given work load, possibly similar to long-acting nitrate therapy. Systolic blood pressure at the 20 mg dose of nifedipine (but not at the 10 mg dose) was significantly lower than that with placebo but caused little reflex increase in heart rate.

817 Effect of Nifedipine on Myocardial Ischemia: Analysis of Collateral Flow, Pulsatile Heart and Regional Muscle Shortening
PHILIP D. HENRY, RAFAEL SHUCHLEIB, RICHARD E. CLARK and JULIO E. PEREZ

In dogs subjected to coronary ligation myocardial ischemia reduced the amplitude of the pulse signals, the mean intramyocardial temperature and the amplitude of the intramyocardial cold transients detected after the injection of cold saline solution. Nifedipine partly reversed all thermal changes due to ischemia, increased collateral perfusion and decreased resistance in the coronary bed distal to the occlusion. These and other results indicate nifedipine increases collateral flow to the acutely ischemic myocardium and enhances contractile performance. With nifedipine the protective action on the ischemic myocardium rather than a cardioplegic effect limiting the metabolic needs of the myocardium at risk appears to be the most important factor in limiting the extent of ischemic injury to the myocardium.

825 Nifedipine: A Myocardial Protective Agent
RICHARD E. CLARK, IGNACIO Y. CHRISTLIEB, PHILLIP D. HENRY, ALBERT E. FISCHER, JOHN D. NORA, JOSEPH R. WILLIAMSON and BURTON E. SOBEL

This summary of experimental experiences in rabbits and dogs with nifedipine indicates that this drug was effective in protecting myocardial performance and structure after 2 hours of global ischemia during hypothermic cardiopulmonary bypass. Nifedipine exerted a beneficial effect on postischemic myocardial stiffness and mitochondrial calcium accumulation. This agent may prove useful as an adjunct to cold cardioplegia in man for enhanced myocardial protection during cardiac surgery.

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832 **Effects of Nifedipine After Intravenous and Intracoronary Administration**
MARTIN KALTENBACH, WOLFGANG SCHULZ and GISBERT KOBER

These studies in patients with angina pectoris show the antianginal action of an intravenous dose of 1.0 mg of nifedipine is comparable with a sublingual dose of 20 mg. Its antianginal activity continues for more than 1 hour but is not related to the short-lasting increase in total coronary blood flow. The mode of action of this calcium antagonist drug must include a central cardiac effect most likely related to activation of the calcium-mediated myocardial contraction process leading to reduced oxygen requirements of the heart. No serious side effects were observed after intravenous or intracoronary administration of nifedipine in these patients.

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845 **Introduction: Recent Perspectives on Hypertension and the Heart**
ROBERT C. TARAZI

849 **Coronary Pressor Reflexes**
ARTHUR M. BROWN

This succinct review will improve understanding and comprehension of some basic mechanisms involved in the genesis of apparently complex cardiac reflexes. The heart, differing from other cardiovascular reflexogenic structures, has two prominent inputs to the central nervous system. Although historically the vagal input has received the greatest attention, there seems to be no numeric difference between the vagal and spinal inputs with respect to afferent fibers relaying information to the central nervous system. The spinal input, mediated by afferent cardiac sympathetic nerve fibers, mainly produces reflex pressor effects; the medullary input, mediated by afferent vagal fibers, mainly produces more reflex depressor effects. Currently available evidence indicates the reflex effects of excitation of the vagal input are mainly inhibitory whereas the reflex effects of afferent sympathetic excitation are mainly excitatory.

852 **Anatomic and Physiologic Considerations of a Cardiogenic Hypertensive Chemoreflex**
THOMAS N. JAMES, GILBERT R. HAGEMAN and FERDINAND URTHALER

Attention is directed to the anatomic and physiologic aspects of the cardiogenic hypertensive chemoreflex originating within chemoreceptor tissue lying between the aorta and pulmonary artery in human and canine hearts. This tissue receives its blood supply from the proximal left coronary circulation. The afferent pathway of the reflex is through the vagus nerve and its efferent paths include both vagal and sympathetic branches. In the dog this tissue is the site of origin for a powerful hypertensive reflex stimulated by serotonin. Despite a body of indirect evidence, however, there is as yet no direct proof that the cardiogenic hypertensive chemoreflex exists in man. Such indirect evidence is discussed in this fascinating new perspective on many important questions in experimental and clinical biology associated with this cardiogenic hypertensive chemoreflex.

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860 Positive Feedback Sympathetic Reflexes and Hypertension
ALBERTO MALLIANI, MASSIMO PAGANI and MARIO BERGAMASCHI

A pressor reflex can be elicited from the descending thoracic aorta with its sympathetic sensory innervation in dogs. This reflex constitutes a positive feedback mechanism that interacts with the sinoaortic and other positive feedback mechanisms that in turn interact with other negative feedback control systems in the regulation of arterial blood pressure. The pulsatile stretch of the aortic wall is probably the most effective excitatory stimulus. In anesthetized cats aortic stretch induced significant increases in arterial blood pressure, heart rate and maximal rate of increase in left ventricular pressure which could be differentially abolished by alpha or beta receptor blockade. There are some physiologic conditions, such as exercise, in which the efferent sympathetic activity seems to escape restriction. Arterial hypertension, as a disease of regulation, could partly be the result of an increased sympathetic efferent tone that may depend not only on an augmented central command, but also on the peripheral action of sympathetic loops exhibiting positive feedback characteristics.

866 Possible Role of Cardioaortic Reflexes in Postcoronary Bypass Hypertension
FETNAT M. FOUAD, F. G. ESTAFANOUS, EMMANUEL L. BRAVO, KAMALNATH A. IYER, JOHN H. MAYDAK and ROBERT C. TARAZI

Hemodynamic and humoral studies in 85 patients with postcoronary bypass hypertension in the immediate postoperative period showed that the increase in blood pressure was associated with an elevation in systemic vascular resistance and tachycardia while the increase in mean arterial pressure correlated significantly with changes in plasma catecholamine levels. Unilateral stellate block controlled hypertension in 81 percent of patients. These results suggest that postcoronary bypass hypertension could be related to an increase in total peripheral resistance, which in turn is related to an afferent sympathetic reflex originating from the heart, great vessels or coronary arteries. Stellate block appears advisable only when a reflex cause is considered after other obvious and remediable causes are excluded. In this study careful administration of nitroprusside was effective when most other measures failed to relieve the hypertension.

873 Cardiac Receptors: Normal and Disturbed Function
DAVID E. DONALD and JOHN T. SHEPHERD

The heart contains numerous mechanoreceptors that are activated by systolic and diastolic events and are capable of modulating the arterial blood pressure through reflex adjustment of heart rate and contractility and of the caliber of the systemic blood vessels. Both the cardiac and arterial mechanoreceptors can modulate the output of renin from the kidney but the cardiac mechanoreceptors are more sensitive to small changes in blood volume. There is some evidence that the bradycardia resulting from digitalis therapy in man may be caused in part by excitation of vagally innervated left ventricular receptors. The cardiovasuclar response to coronary occlusion represents a balance between the effects of a decrease in carotid sinus inhibition and an increase in the depressor influence of the cardiac receptors.

879 Atrial Reflexes and Renal Function
RONALD J. LINDEN

These dog experiments clearly demonstrate that the increase in heart rate, urinary flow and sodium excretion after distension of small balloons in the venous atrial function of the heart is caused by a reflex from atrial receptors. The afferent limb is the vagi nerves and the efferent pathway is nervous and hormonal. Stimulation of atrial receptors reduces the activity in nerves to the kidney, which increases both urinary volume and sodium excretion and releases a blood-borne agent, probably a diuretic substance, that increases urinary volume without affecting sodium excretion.

884 Cardiac Reflexes in Normotensive and Spontaneously Hypertensive Rats
PETER THOREN, EDDY NORESSON and SVEN-ERIK RICKSTEN

In spontaneously hypertensive rats the cardiac receptors are reset to operate at a higher pressure level, the left atrial pressure is chronically elevated, the thresholds of the receptor endings are twice as high as in normotensive rats and, at a 10 percent increase in blood volume, splanchnic outflow is more significantly decreased. The mechanism underlying such a hyperreactive volume receptor response is unknown but a less distensible venous system may be contributory.

889 Reflex Control of the Heart
PETER SLEIGHT

This review presents evidence that baroreflex control of the heart, as shown by the Oxford phenylephrine methods of testing and the newer noninvasive neck cuff methods, is impaired in hypertensive persons. The baroreflex in such persons is

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because INDERAL, alone or in combination with other agents, has established a remarkable record of blood pressure control. Another encouraging sign: increased dosage usually does not produce proportional decreases in heart rate.

Proper patient selection is important: INDERAL should be employed only in the absence of congestive heart failure, sinus bradycardia, or heart block greater than first degree.*

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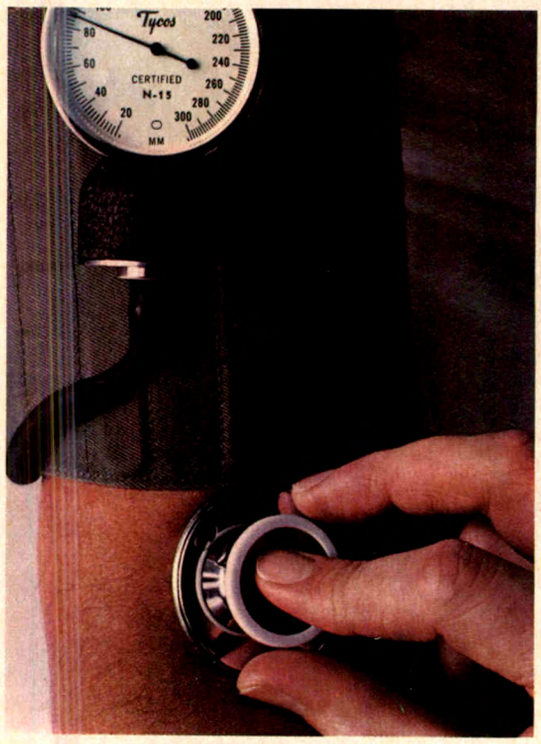

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BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR)
Inderal® BRAND OF
propranolol hydrochloride
A beta-adrenergic blocking agent

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

ACTIONS

The mechanism of the antihypertensive effects of INDERAL has not been established. Among the factors that may be involved in the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain.

Propranolol hydrochloride decreases heart rate, cardiac output, and blood pressure. Although total peripheral vascular resistance may increase initially, it readjusts to the pretreatment level, or lower, with chronic usage. Earlier studies indicate that plasma volume remains unchanged or may decrease. However, there are certain more recent studies suggesting that in the absence of sodium restriction, plasma volume may increase.

INDICATIONS

Hypertension
INDERAL is indicated in the management of hypertension. It is usually used in combination with other drugs, particularly a thiazide diuretic. INDERAL is not indicated for treatment of hypertensive emergencies.

CONTRAINDICATIONS

INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.*, that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by INDERAL's negative inotropic effect. The effects of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, INDERAL therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.*, isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose.

PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory: bronchospasm

Hematologic: agranulocytosis, nonthrombocytopenic purpura; thrombocytopenic purpura

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DOSAGE AND ADMINISTRATION

ORAL

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 40 mg INDERAL twice daily, whether used alone or added to a diuretic. Dosage may be increased gradually until adequate blood pressure is achieved. The usual dosage is 160 to 480 mg per day. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower doses are used, may experience a modest rise in blood pressure toward the end of the 12 hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, or 3 times daily therapy may achieve better control.

PEDIATRIC DOSAGE

At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

INTRAVENOUS

The intravenous administration of INDERAL has not been evaluated adequately in the management of hypertensive emergencies.

OVERDOSAGE OR EXAGGERATED RESPONSE

IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg): IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY.

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS.

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both reset to a higher level and has diminished gain. This latter change is important in the vicious circle of hypertension because it is likely to lead to slower and less effective buffering of increases in pressure.

895 Control of Blood Pressure by Carotid Sinus Baroreceptors in Human Beings
GIUSEPPE MANCIA, ALBERTA FERRARI, LUISA GREGORINI, GIANFRANCO PARATI, MARIA CARLA FERRARI, GUIDO POMIDOSSI and ALBERTO ZANCHETTI

This study reviews some technical aspects of the use of a variable pressure neck chamber and the influence carotid baroreceptors exert on arterial blood pressure in normotensive subjects and in those with essential hypertension. In human hypertension the carotid baroreflex mechanism controlling blood pressure undergoes a very marked resetting but no major reduction in sensitivity. The depressor response to an increase in carotid baroreceptor activity depends on both a reduction in cardiac output and a systemic vasodilatation. Peripheral vasoconstriction is the only factor accounting for the pressor response to reduced baroreceptor activity. The asymmetry of the blood pressure responses to increases and decreases in carotid baroreceptor activity reveals an inherent property of the carotid baroreceptor function in human beings. This reflex mechanism can provide normotensive persons with a better antihypotensive than antihypertensive action.

903 Integration of Reflex Responses in the Control of Blood Pressure and Vascular Resistance
FRANCOIS M. ABBOUD

This overview emphasizes four important concepts related to integration of cardiovascular reflexes and discusses their clinical implications: (1) Activation of sympathetic efferent activity to various organs is selective and nonuniform. (2) When two groups of sensory afferents causing opposing responses are activated simultaneously, the effect of one sensory afferent system will override the other. (3) The reflex response to activation of one group of sensory afferents may depend on the input from other groups of afferents to the medullary neurons. (4) Stimulation of sensory afferent receptors may be modified by drugs or humoral factors acting on the receptor itself or on the chemical and mechanical characteristics of the tissues surrounding the receptor. The cardiopulmonary baroreceptors appear to be sensitized by acetylstrophanthidin. This sensitization may explain in part the action of digitalis on the peripheral circulation in heart failure.

912 Overview of Cardiovascular Reflexes in Hypertension
ALBERTO ZANCHETTI

This interim perspective on the problem of cardiovascular reflexes in hypertension today draws attention to the yet unanswered questions concerning the "horse and cart" relation of these reflexes and hypertension: (1) Can alterations in cardiovascular reflexes initiate a persistent rise in arterial pressure? (2) Is it an alteration in depressor or in pressor that really matters in hypertension? (3) What is the nature of the reflex alterations that actually occur in hypertension? Various interpretations of the available experimental data are presented in an effort to explain these relations by reasonable hypotheses that require additional study. Genetic factors also play an important role in determining arterial pressure levels. It remains to be more firmly established whether sympathetic activity and its reflex influences on the cardiovascular system are inherited and to what degree.

919 Morphometry of Cardiac Hypertrophy Induced by Experimental Renal Hypertension
JOSEPH WIENER, FILIBERTO GIACOMELLI, ALDEN V. LOUD and PIERO ANVERSA

Using a technique based on nuclear counts per unit area in tissue slices of different known thicknesses to determine the mean volume of cells within the left ventricle of normal and hypertensive rats, these investigators found the morphometric characteristics of myocytes from hypertensive rats are significantly different from normal and significant differences occur between the inner and outer layers of the myocardium for practically every cytoplasmic component. The epicardial region enlarged 37 percent with proportional increases of myocyte and interstitial volumes; the endocardial enlargement was only 26 percent, consisting of 21 percent hypertrophy of myocytes and a 55 percent increase in interstitial components. The cell reaction in cardiac hypertrophy is one in which myofibril, smooth endoplasmic reticulum and T system growth significantly exceeds the mean cell growth whereas nuclear, mitochrondrial and matrix growth is relatively much less. In hypertension the volume of the T system increased 62 percent in endocardial myocytes and 99 percent in those of the epicardium.

930 Echocardiographic Dimensions in Borderline and Sustained Hypertension
M. E. SAFAR, J. P. LEHNER, M. I. VINCENT, M. T. PLAINFOSSE and A. Ch. SIMON

Echocardiographic dimensions and hemodynamic indexes in 42 patients with borderline hypertension showed a signifi-

Continued on page A21

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cantly increased thickness of the interventricular septum (IVS), a normal posterior wall (PW) thickness and a significantly elevated IVS/PW ratio that correlated negatively with the cardiac index and positively with the preejection period. In 22 patients with sustained hypertension, symmetric cardiac hypertrophy and a significant positive correlation between the IVS/PW ratio and diastolic pressure were observed. The preponderance of asymmetric septal hypertrophy and increased IVS/PW ratio in patients with borderline hypertension was unexpected. The association of these changes with signs of enhanced sympathetic activity suggests some role for the autonomic nervous system in producing them in the patients with borderline hypertension. In sustained hypertension the symmetric cardiac hypertrophy was secondary to a progressive increase in pressure load.

936 Left Ventricular Mass and Wall Thickness in Hypertension. Comparison of M Mode and Two Dimensional Echocardiography in Two Experimental Models

ERNESTO E. SALCEDO, KRZYSZTOF GOCKOWSKI and ROBERT C. TARAZI

These direct anatomic-echocardiographic correlations of ventricular wall thickness and mass in 33 normotensive dogs and in 10 dogs with experimental hypertension confirmed the need to evaluate echocardiographic measurements in different models of disease. The cube formula was accurate in many normotensive dogs but less accurate in dogs with experimental hypertension and irregular thickening of left ventricular walls. Two dimensional echocardiography significantly increased the accuracy of calculated mass and was useful in defining the presence of left ventricular hypertrophy in dogs with experimental hypertension and increased thickness of the anterolateral wall with little change in the septal and posterior walls. These results suggest evaluation of left ventricular changes in hypertension cannot depend on M mode echocardiography alone.

941 Cardiac Hypertrophy: Its Characteristics As a Growth Process

RADOVAN ZAK, AKIRA KIZU and LAWRENCE BUGAISKY

This review of the causal relation between changing cardiac function and growth at the cell level concludes that the appearance of cell-specific proteins and of spontaneous contractions (the earliest stage of cardiac morphogenesis) is independent of hemodynamic forces, and looping (the first major morphologic transformation of the primitive heart) is an intrinsic property of the heart. Subsequent hemodynamic function is closely coupled to cardiac growth and the size of the adult heart closely matches the hemodynamic requirements typical of the environmental adaptation of a given animal. In contrast to most other cells, the myocytes of the adult myocardium have never been unequivocally shown to resume mitosis secondary to either injury or induced growth. In human heart disease the addition of new muscle cells supplements cell hypertrophy if there is extreme enlargement.

947 Functional Significance of Altered Myosin Adenosine Triphosphate Activity in Enlarged Hearts

NORMAN R. ALPERT, LOUIS A. MULIERI and RAYE Z. LITTEN

These experiments using rapid myothermal measurements in rabbits whose hearts were enlarged secondary to pressure overload (by pulmonary arterial banding) or thyrotoxic stress (by daily injections of L-thyroxine) showed in vitro actin-activated adenosine triphosphatase activity levels were 70 and 175 percent of normal for the pressure-overloaded and thyrotoxic hearts, respectively; the tension-dependent hearts per unit tension in the same preparations were, respectively, 78 and 154 percent of normal. These data suggest a reasonable correlation between the in vivo and in vitro measurements of contractile protein adenosine triphosphatase activity. Further analysis indicates in pressure overload hypertrophy adaptation involves a decrease in the crossbridge cycling rate, an increase in crossbridge off-time and an increase in the on-time of the crossbridge. For thyrotoxic hypertrophy the adaptation involves an increase in the cycling rate, a decrease in the off-time and a decrease in the on-time.

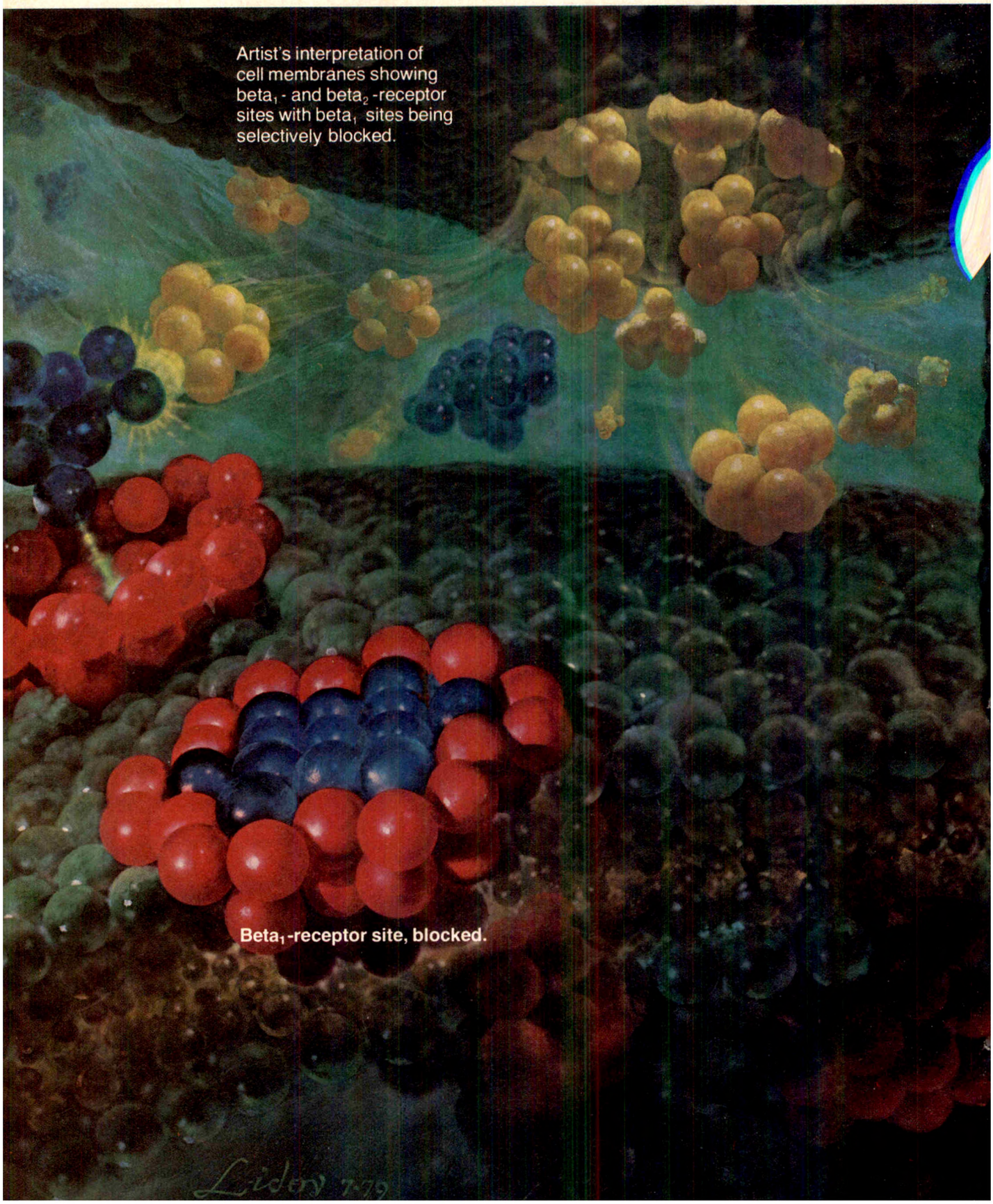
954 Collagen Synthesis in Development and Reversal of Cardiac Hypertrophy in Spontaneously Hypertensive Rats

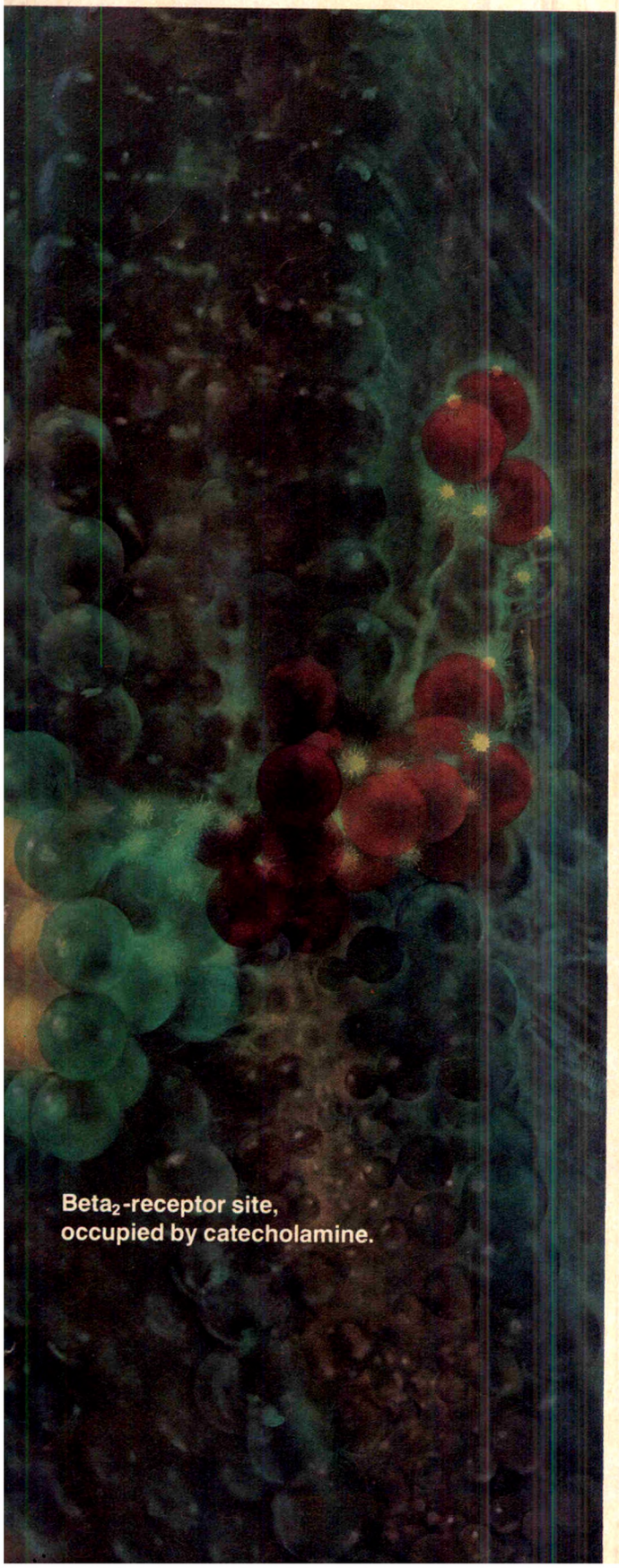
SUBHA SEN and F. MERLIN BUMPUS

These studies demonstrate an intriguing dissociation in collagen synthesis in the myocardium between younger and older spontaneously hypertensive rats. The increased rate of collagen synthesis at 4 and 8 weeks was independent of the rise in blood pressure; in contrast, in the older animals its increase in parallel with increased blood pressure could be successfully prevented by long-term antihypertensive therapy which also reversed myocardial hypertrophy. In young rats the stimulus to increase in collagen may be a humoral factor, a hemodynamic alteration or a genetic factor. In the older hypertensive rats hypertension seemed more important in altering collagen synthesis.

Continued on page A25

the preferential effect





Beta$_2$-receptor site, occupied by catecholamine.

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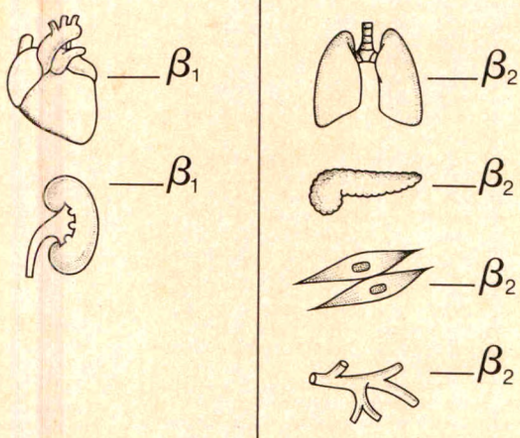
Unlike the nonselective beta blocker, propranolol, which indiscriminately blocks both beta$_1$ and beta$_2$ adrenoreceptors, Lopressor is relatively selective, that is, it exerts a preferential effect on beta$_1$ receptors in the heart—those involved in lowering blood pressure. Lopressor, at usual therapeutic doses, has a much lower affinity for beta$_2$ receptors.

Beta$_1$-and beta$_2$-receptor sites



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*Hansson L, Werkö L: Beta-adrenergic blockade in hypertension. Am Heart J 93(3):394-402 (Mar.) 1977.

Please see next page for brief prescribing information.

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Very well tolerated

- unlike traditional sympathetic inhibitors, there is usually no sedation, sexual dysfunction or postural hypotension with Lopressor
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The most frequently reported adverse reactions (which occurred in approximately ten out of 100 patients) are tiredness and dizziness. Depression and diarrhea have occurred in about five out of 100. Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure.

Lopressor®
metoprolol tartrate

An antihypertensive
beta-blocking agent

Brief Summary of Prescribing Information

Indications Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage in Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.

Allergic: Pruritus has occurred in less than 1 of 100 patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopressor should be individualized. The usual initial dose is 50 mg twice daily whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. Usual maintenance dosage is approximately 100 mg twice a day, with a range of 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower dosages are used, will experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, or three times daily therapy, may achieve better control. Beta$_1$ selectivity diminishes as dosage of Lopressor is increased.

This drug should be stored at controlled room temperature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

Store at controlled room temperature and protect from moisture.

Dispense in tight, light-resistant container (USP).

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For complete details, including description, clinical pharmacology and overdosage, please see full prescribing information.

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CONTENTS

959 **Is Arterial Pressure the Sole Factor Responsible for Hypertensive Cardiac Hypertrophy?**
EDWARD D. FROHLICH and ROBERT C. TARAZI

The heart responds physiologically and biochemically to increased work demand. In hypertension increased arterial pressure is the major stimulus to cardiac hypertrophy, but other mechanisms—including genetic factors, aging, cardiopathy and the adrenergic and renin-angiotensin systems—may also be involved. Both laboratory and clinical data support Meerson's concept that the process of cardiac hypertrophy follows the physiologic needs of the myocardium. Ultimately, however, myocardial contractility may be impaired, which may result in reduced systemic tissue perfusion and cardiac failure. Additional studies are needed to determine the relative importance of the different mechanisms in the development of hypertensive cardiac hypertrophy.

964 **Cardiac Hypertrophy in Early Hypertension**
YUKIO YAMORI, CHUZO MORI, TOSHIKAZU NISHIO, AKIRA OOSHIMA, RYOICHI HORIE, MICHIYA OHTAKA, TAKESHI SOEDA, MASAKAZU SAITO, KATSUTOSHI ABE, YASUO NARA, YASUJI NAKAO and MASAHIRO KIHARA

Vectorcardiographic patterns of left ventricular hypertrophy in prehypertensive stroke-prone rats at the age of 30 to 40 days when the systolic blood pressure was still only 130 to 140 mm Hg suggest that hypertrophy is developing quite early in life and that factors other than blood pressure may be responsible. This structural alteration may be related to or linked with a genetic predisposition to hypertension or could be evoked or accentuated by hypertensive mechanisms already active before the development of overt hypertension. Early detection of left ventricular hypertrophy may be a useful indicator of the incipient stage of structural vascular changes in genetic hypertension. Echocardiographic studies in more than 350 children aged 6 to 15 years showed that 5 of 77 subjects with borderline hypertension had a left ventricular mass clearly above 2 standard deviations of normal for their age. If documented in man, "cardiac hypertrophy in prehypertension" would have important diagnostic and prognostic implications.

970 **Hypertrophy in the Denervated Heart: A Comparison of Central Sympatholytic Treatment With 6-Hydroxydopamine and Peripheral Sympathectomy With Nerve Growth Factor Antiserum**
SUZANNE OPARIL and ANTHONY F. CUTILLETTA

These data demonstrate that destruction of the central catecholaminergic structures by centrally administered 6-hydroxydopamine and peripheral sympathectomy by nerve growth factor antiserum in immature spontaneously hypertensive rats prevent the development of hypertension by different physiologic mechanisms but do not alter the suppressed ventricular function, the increased peripheral resistance or the development of myocardial hypertrophy. The hemodynamic abnormalities and myocardial hypertrophy seen in these rats may be determined by factors independent of the blood pressure, but increased sympathetic activity appears necessary for the development of hypertension in spontaneously hypertensive rats.

979 **Cardiac Pumping Ability in Rats With Experimental Renal and Genetic Hypertension**
CARLOS M. FERRARIO, MICHELLE M. SPECH, ROBERT C. TARAZI and YOSHITAKA DOI

These experiments in rats with established hypertension indicate that hemodynamic and structural factors contribute to alterations in cardiac function during the chronic established phase of arterial hypertension. Prolonged treatment with methyldopa (3 to 6 weeks) normalized arterial pressure, reversed cardiac hypertrophy and improved ventricular pumping ability in terms of both peak stroke volume and cardiac output. The improved performance after methyldopa was in part due to reduced impedance to ventricular ejection.

986 **Hemodynamic Consequences of Left Ventricular Hypertrophy in Spontaneously Hypertensive Rats**
MARGARETA HALLBÄCK-NORDLANDER, EDDY NORESSON and PETER THOREN

In vitro studies show isolated, perfused hearts from spontaneously hypertensive rats exhibit a rightward shift of the Frank-Starling curve in the lower range of filling pressures up to 10 mm Hg. The extent of this shift is proportional to the degree of left ventricular hypertrophy. This shift of the Frank-Starling curve is a consequence of an altered relation between end-diastolic tension in the thick-walled ventricle. The hypertrophy implies that the left ventricle copes more efficiently with increases in afterload, provided the diastolic prestretch is adequate. Maximal cardiac performance appears better in spontaneously hypertensive rats than in normotensive rats at increased levels of afterload. A relative "hyporeactivity" of the capacitance vessels also suggests an altered relation between cardiac filling pressure and stroke volume of the hypertrophied left ventricle in the spontaneously hypertensive rat.

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994 Alterations of Cardiac Performance in Rats With Established Spontaneous Hypertension
JANICE PFEFFER, MARC PFEFFER, PETER FLETCHER and EUGENE BRAUNWALD

This comparison of cardiac performance in age-matched normotensive and spontaneously hypertensive rats of both sexes shows greatly diminished ventricular performance in old female and male hypertensive rats. In 18 month old hypertensive rats the reduced stroke volume was delivered from a normal end-diastolic volume so that the ejection fraction index was only moderately reduced; in old male hypertensive rats a reduced peak stroke volume was ejected from a ventricle that was significantly dilated at the high distending pressures that occurred during volume loading so that the ejection fraction index was substantially reduced. Maximal acceleration of aortic blood flow significantly decreased in 18 month old female hypertensive rats and even more in the 18 month old male hypertensive rats. Systolic function decreased in old hypertensive rats. Hypertrophic growth of the left ventricle in the aging hypertensive rat is associated with both a compensated and depressed phase of cardiac performance.

999 Ventricular Function and Coronary Hemodynamics in Hypertensive Heart Disease
BODO-ECKEHARD STRAUER

Analysis of left ventricular function wall geometry and coronary hemodynamics and myocardial energy demand in 114 patients with essential hypertension revealed left ventricular function was normal in patients with hypertensive hypertrophy but impaired in the presence of regional contraction abnormalities or ventricular dilatation. In these patients coronary blood flow (+18 percent), coronary resistance (+38 percent) and myocardial oxygen consumption (MVO_2) (+21 percent) were increased and coronary reserve reduced even in hypertensive hypertrophy without coronary artery disease. At least two types of inappropriate left ventricular hypertrophy were noted: (1) low stress hypertrophy, with an increased mass to volume ratio, normal left ventricular function and normal or reduced MVO_2; and (2) high stress hypertrophy, with normal or low mass to volume ratio, impaired left ventricular function and increased MVO_2. The appropriateness of left ventricular hypertrophy, as a result of mass to volume ratio and stress, is a major determinant of left ventricular performance and of myocardial oxygen consumption.

1007 Cardiac Load and Function in Hypertension. Ultrasonic and Hemodynamic Study
MAURIZIO GUAZZI, CESARE FIORENTINI, MARIA T. OLIVARI and ALVISE POLESE

Echocardiographic measurements of the heart in 46 patients with established uncomplicated primary hypertension permitted separation of those with a normal-sized heart (Group I, 13 patients) from those with left ventricular concentric hypertrophy (Group II, 19 patients) and left ventricular hypertrophy and enlargement (Group III, 14 patients). The function of both right and left ventricles was maintained in Group I, augmented in Group II and reduced in Group III. Echocardiography provides more frequent positive findings of concentric hypertrophy than electrocardiography or chest roentgenography. The improved right ventricular function in Group II and the depressed function in Group III are best explained by changes in the contractile state that involve both sides of the heart.

1013 Renin, Aldosterone and Cardiac Decompensation: Studies With an Oral Converting Enzyme Inhibitor in Heart Failure
ROBERT C. TARAZI, FETNAT M. FOUAD, JOANNE K. CEIMO and EMMANUEL L. BRAVO

Experience with the use of captopril, an oral converting enzyme inhibitor, given to six normotensive patients with refractory heart failure suggests this drug could be helpful in heart failure by reducing both peripheral resistance and plasma aldosterone levels. The response to captopril revealed (1) an apparent dichotomy between hemodynamic effects and clinical improvement, and (2) a marked reduction in plasma aldosterone levels. Changes in cardiac output and stroke volume were minor. Long-term clinical improvement included fewer symptoms, loss of weight and greater capacity for exercise. Plasma renin activity increased in all but one patient. The plasma aldosterone level was reduced in all.

1019 Role of Vasoconstrictor Mechanisms in the Control of Left Ventricular Performance of the Normal and Damaged Heart
JAY N. COHN, IWAO MASHIRO, T. BARRY LEVINE and JAWAHAR MEHTA

The normal ventricle compensates for changes in impedance largely by changes in preload, but the damaged heart loses this compensatory ability and its stroke volume becomes inversely related to outflow resistance. In these damaged hearts the emergence of a stroke volume dependence on aortic impedance can be attributed at least in part to loss of a brisk Frank-Starling mechanism to counteract the normal influence of impedance on ejection fraction. Observations on patients with heart failure have clearly demonstrated the salutary nonspecific vasodilation of drugs that reduce aortic impedance. Inappropriate vasoconstriction in heart failure resulting from stimulation of the sympathetic or renin-angiotensin system may respond to blockade of the formation of angiotensin II in some patients. Preliminary experience with captopril, an oral angiotensin converting enzyme inhibitor, in patients with severe heart failure indicates that the hemodynamic response is maintained and clinical improvement occurs.

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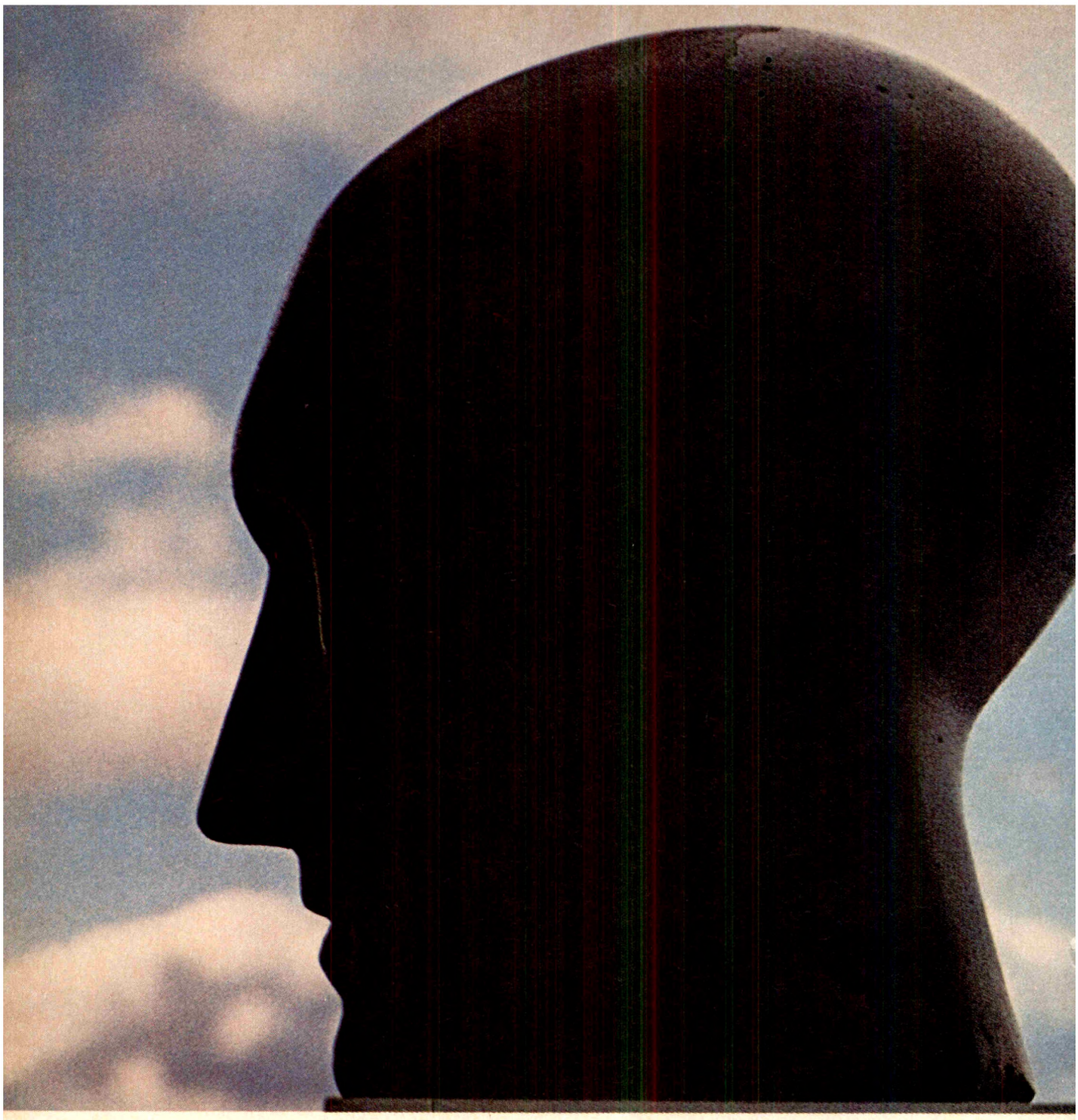
1023 Effects of Cardiac Hypertrophy Secondary to Hypertension on the Coronary Circulation
MELVIN L. MARCUS, THOMAS M. MUELLER, JOSEPH A. GASCHO and RICHARD E. KERBER

This review on the effects of hypertrophy on the coronary circulation when the supply/demand ratio is within the normal range concludes that cardiac hypertrophy adversely affects the coronary circulation. Blood flow per gram in hypertrophied ventricles is normal at rest but coronary vascular resistance is greatly increased when hypertension is the cause of left ventricular hypertrophy. Transmural distribution of myocardial perfusion is often abnormal and maximal coronary vasodilatation is limited substantially. Newly developed techniques for estimating transmural and phasic coronary blood flow now make it possible to extend similar studies to patients with cardiac hypertrophy.

1029 Effects of Exercise on Blood Flow in the Hypertrophied Heart
ROBERT J. BACHE and THOMAS R. VROBEL

Comparing the response of regional myocardial blood flow to exercise in normal dogs and in dogs with left ventricular hypertrophy produced by perinephritic hypertension, this study failed to demonstrate any exercise-induced perfusion defect within the hypertrophic left ventricle. The animals in this study showed a normal ability to increase myocardial blood flow during exercise and there was no evidence of impaired coronary perfusion. The data indicate that heart rate and the product of heart rate and systolic blood pressure may be used to predict myocardial blood flow during exercise in the dog with left ventricular hypertrophy just as in the normal dog heart.



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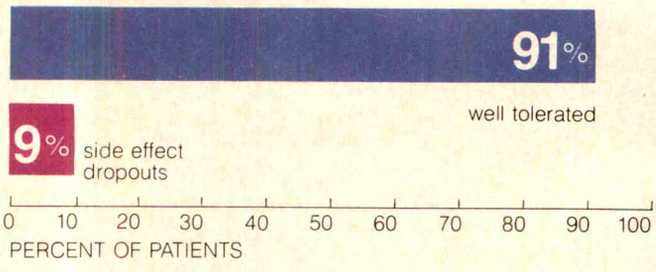

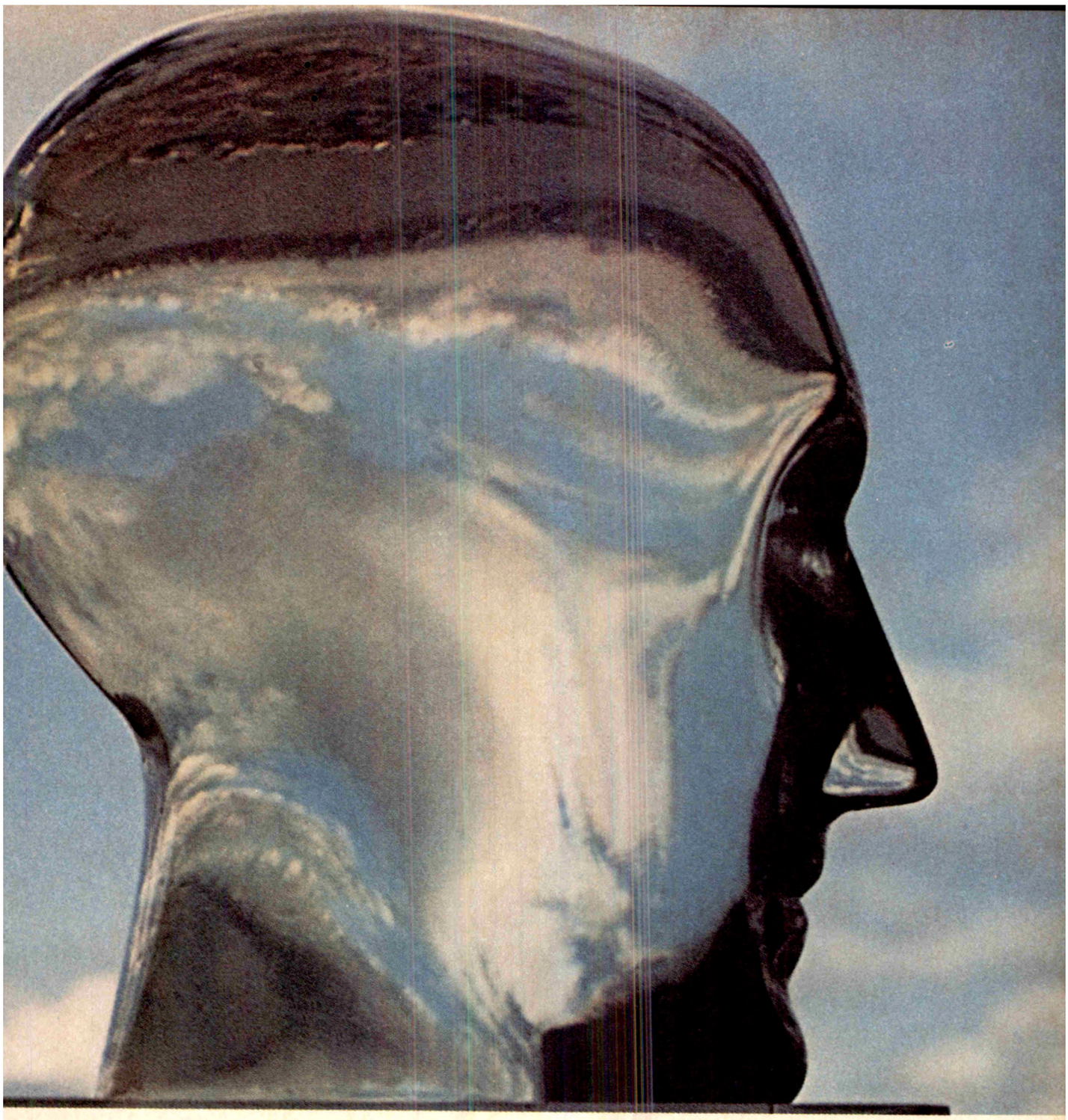

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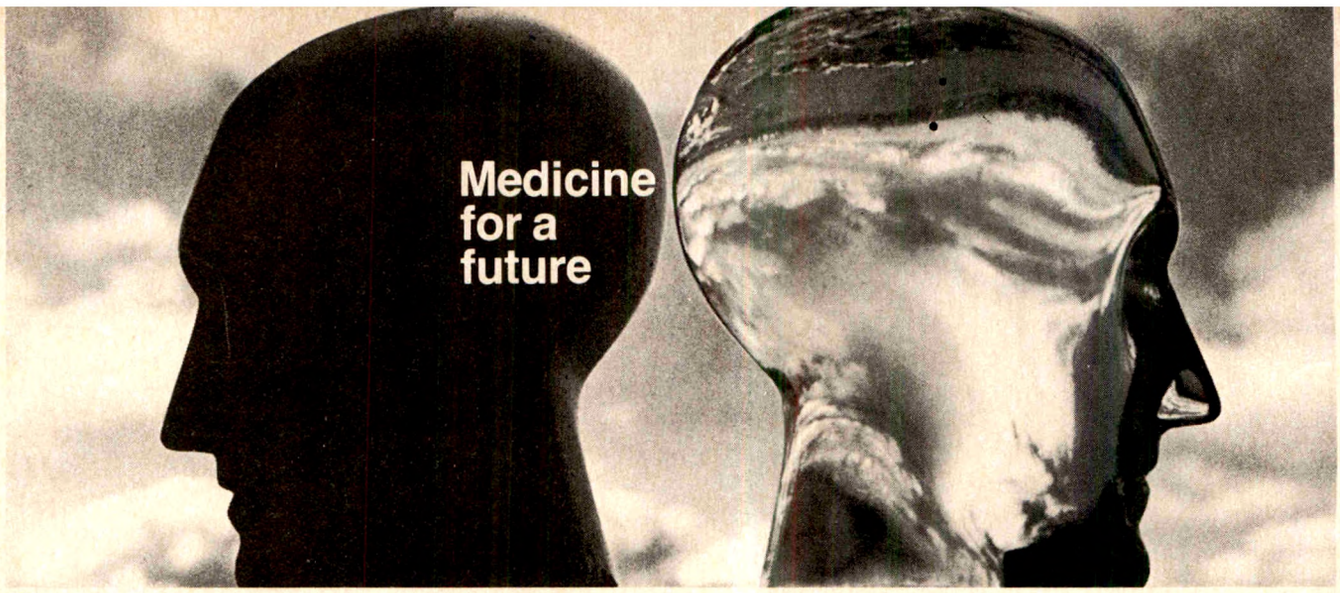

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Usage in Pregnancy: In view of embryotoxicity findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefit outweighs the potential risk to mother and fetus.

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Precautions: When discontinuing Combipres, reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of Combipres therapy or by intravenous phentolamine.

Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect of the clonidine hydrochloride component.This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other antihypertensive agent, Combipres should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Combipres should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmological findings have been recorded with Catapres, in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Patients predisposed toward or affected by diabetes should be tested periodically while receiving Combipres, because of the hyperglycemic effect of chlorthalidone.

Because of the possibility of progression of renal failure, periodic determination of the BUN is indicated. If, in the physician's opinion, a rising BUN is significant, the drug should be stopped.

The chlorthalidone component of Combipres may lead to sodium and/or potassium depletion. Muscular weakness, muscle cramps, anorexia, nausea, vomiting, constipation, lethargy or mental confusion may occur. Severe dietary salt restriction is not recommended in patients receiving Combipres.

Periodic determinations of the serum potassium level will aid the physician in the detection of hypokalemia. Extra care should be given to detection of hypokalemia in patients receiving adrenal corticosteroids, ACTH or digitalis. Hypochloremic alkalosis often precedes other evidence of severe potassium deficiency. Frequently, therefore, more sensitive indicators than the potassium serum level are the serum bicarbonate and chloride concentrations. Also indicative of potassium depletion can be electrocardiographic alterations such as changes in conduction time, reduction in amplitude of the T wave; ST segment depression; prominent U wave. These abnormalities may appear with potassium depletion before the serum level of potassium decreases. To lessen the possibility of potassium deficiency, the diet, in addition to meat and vegetables, should include potassium-rich foods such as citrus fruits and bananas. If significant potassium depletion should occur during therapy, oral potassium supplements in the form of potassium chloride (3 to 4.5 gm/day), fruit juice and bananas should be given.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy.

Clonidine hydrochloride: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one case of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash; impotence, urinary retention; increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Chlorthalidone: Symptoms such as nausea, gastric irritation, anorexia, constipation and cramping, weakness, dizziness, transient myopia and restlessness are occasionally observed. Headache and impotence or dysuria may occur rarely. Orthostatic hypotension has been reported and may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics. Skin rashes, urticaria and purpura have been reported in a few instances.

A decreased glucose tolerance evidenced by hyperglycemia and glycosuria may develop inconsistently. This condition, usually reversible on discontinuation of therapy, responds to control with antidiabetic treatment. Diabetics and those predisposed should be checked regularly.

As with other diuretic agents hypokalemia may occur (see Precautions). Hyperuricemia may be observed on occasion and acute attacks of gout have been precipitated. In cases where prolonged and significant elevation of blood uric acid concentration is considered potentially deleterious, concomitant use of a uricosuric agent is effective in reversing hyperuricemia without loss of diuretic and/or antihypertensive activity.

Idiosyncratic drug reactions such as aplastic anemia, thrombocytopenia, leukopenia, agranulocytosis, and necrotizing angiitis have occurred, but are rare.

The remote possibility of pancreatitis should be considered when epigastric pain or unexplained gastrointestinal symptoms develop after prolonged administration.

Other adverse reactions which have been reported with this general class of compounds include: jaundice, xanthopsia, paresthesia and photosensitization.

Overdosage: *Catapres (clonidine hydrochloride):* Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals abolishes all effects of Catapres overdosage.

Chlorthalidone: Symptoms of overdosage include nausea, weakness, dizziness, and disturbances of electrolyte balance. There is no specific antidote, but gastric lavage is recommended, followed by supportive treatment. Where necessary, this may include intravenous dextrose and saline with potassium administered with caution.

How Supplied: Combipres* 0.1 (Each tablet contains clonidine hydrochloride 0.1 mg + chlorthalidone 15 mg). It is available as pink, oval, single-scored compressed tablets in bottles of 100.

Combipres* 0.2 (Each tablet contains clonidine hydrochloride 0.2 mg + chlorthalidone 15 mg). It is available as blue, oval, single-scored compressed tablets in bottles of 100.

For complete details, please see full prescribing information.

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SYMPOSIUM ON NIFEDIPINE AND CALCIUM FLUX INHIBITION IN THE TREATMENT OF CORONARY ARTERIAL SPASM AND MYOCARDIAL ISCHEMIA

Bernard Lown, MD, FACC, Guest Editor

Preface

EUGENE J. SAYFIE, MD, FACC

Miami Beach, Florida

The papers that follow were originally presented at a Symposium sponsored by the Miami Heart Institute in March 1979 at the time of the Annual Scientific Session of the American College of Cardiology. We were particularly happy to sponsor this Symposium because of its potential importance.

We have come a long way from the simple and classic description of angina pectoris made by Heberden in 1772 to the hundreds of scientific papers on the current status of our understanding of angina pectoris presented at that Scientific Session. These presentations included studies employing the space age techniques of radioisotope imaging, dynamic echocardiography, telemetric monitoring, exercise testing, invasive arteriography, subcellular histologic examination and biochemical study of the tissues. These techniques were directed toward a better understanding of the etiologic factors and the mechanisms implicated in the production of angina pectoris, myocardial infarction and coronary artery disease and, of course, of their consequences on modern society.

The search for an answer to the treatment of myocardial ischemia and its effect on mortality and morbidity in the United States has led to the proliferation of special coronary care units and to the development of expensive and sophisticated cardiovascular surgical programs in every specialized center in the country. As our knowledge and experience increase, we were able to look back candidly at the effects of our efforts on society and to reevaluate our conclusions on the mechanisms involved in heart disease. Just as we have been trying continually to review critically the efficacy of coronary bypass surgery as a treatment for coronary artery disease in angina pectoris, we also have been reevaluating our conclusions regarding the mechanism of angina pectoris and finding new ways to deal with these mechanisms. Thus, a reexamination of coronary arterial spasm as a cause of myocardial ischemia, angina pectoris and myocardial infarction is appropriate.

Historically, Heberden mentioned nonexertional angina; perhaps this was an early description of the symptom in patients with coronary spasm. Was the tobacco angina described in 1928 by Moskowitz coronary spasm? In the early part of the century, many investigators mentioned this possibility. Parkinson and Bedford spoke of "contraction of coronary arteries." Osler and Lewis also mentioned such mechanisms. Prinzmetal and his co-workers in 1959 described what they called variant angina—nonexertional angina with S-T segment elevation due to coronary spasm—in patients with coronary artery disease. Subsequently, many well documented studies revealed the presence of coronary spasm to be a factor in patients with or without coronary arteriosclerosis, with or without S-T segment elevation or other S-T changes and, in some cases, with or without symptoms of angina pectoris. It seems clear, therefore, that spasm is a factor in the production of myocardial ischemia in our patients. How, then, can we deal with this problem? Through education, research and the treatment of patients—which are our goals at the Miami Heart Institute. We thank our colleagues who came from this country and from others to discuss the problem of nifedipine and calcium flux inhibition in the treatment of coronary arterial spasm and myocardial ischemia and to look at modes of therapy for this particular mechanism of angina pectoris. We must, of course, give special thanks to Pfizer Pharmaceuticals, who have supported our efforts in this area.

From the Miami Heart Institute, Miami Beach, Florida.

Address for reprints: Eugene J. Sayfie, MD, Miami Heart Institute, 4701 North Meridian Avenue, Miami Beach, Florida 33140.

Introduction

BERNARD LOWN, MD, FACC
Chairman and Moderator

Boston, Massachusetts

The first U.S. symposium on nifedipine was assembled barely a few hours after completion of the 28th Annual Scientific Session of the American College of Cardiology at Miami Beach. Yet despite the exposure over 4 days to a veritable Niagara of words, nearly 900 physicians and scientists chose to reconvene in a darkened room for further aural onslaught. The reason for such presumed masochism needs exploration. First, we are dealing with a new class of drugs that partake of a unique mode of action, namely, inhibition of transcellular calcium transport impinging on the relation between excitation-contraction coupling, with profound effects both on vascular smooth muscle and on myocardial inotropism. Second, cardiologists are growing restive at being only technicians in referring patients to the surgical conveyor belt for a costly, but largely palliative solution to the problem of ischemic heart disease. Third, and perhaps most relevant, is the ongoing conceptual crisis in attempting to reconcile the long-standing hemodynamic hypothesis concerning the genesis of ischemic coronary symptoms with numerous contradictory clinical observations.

More than 50 years ago, Keefer and Resnick[1] propounded the current view that angina pectoris is caused by myocardial hypoxia resulting from a mismatch between oxygen and nutrient supply and myocardial metabolic demand. Whereas atherosclerosis imparts a fixed dimension to the conduit delivery system, myocardial demand is modulated by an ever variable work load. This unitary conception was breached when Prinzmetal et al.[2] segregated the small subgroup of patients with variant angina. However, clinicians in practice have long suspected that the issue was not dependent primarly on rusty and obstructed pipes.[3] We need only cite a few of a myriad of examples. To begin with, the severity and frequency of angina pectoris does not correlate well with the extent of vascular disease. Advanced three-vessel coronary atherosclerosis may compromise survival even though the victim never experiences angina. Roberts[4] has shown a similar degree of luminal encroachment in patients with isolated angina pectoris and in those with ischemic heart failure without pain. It is also now well established that typical angina may at times occur in the absence of any angiographically demonstrable coronary disease. MacKenzie[5] first noted at the turn of the century, and thereafter it has been amply confirmed, that with the development of congestive heart failure there is an assuaging or complete disappearance of angina pectoris. The contrary would have been anticipated. Closure of coronary bypass grafts does not always cause recrudescence of anginal symptoms. With advancing age, at least 30 percent of patients will experience complete abatement of anginal symptoms[6] even though it is likely that the atherosclerotic process has increased in severity.

If inadequacy in oxygen delivery in relation to the cardiac work load is the provocative factor, it is difficult to reconcile the striking divergence between the effort required to induce pain on different occasions. A patient may be able to exert himself strenuously indoors without discomfort yet be limited in walking outdoors even though ambient temperatures are similar. Modest activity on first arising in the morning is more likely to precipitate angina than greater exertion later in the day. The threshold for pain is lower with the onset of activity than during its continuance. For example, the golfer afflicted with angina is frequently aware of a strange anomaly—pain is invariable at the initial tee off yet is rare thereafter while he is traversing a more taxing terrain. At times, seemingly innocuous stimuli, minor psychologic stresses or miniscule efforts can set off anginal episodes. Customary work, although arduous, usually does not induce angina. When careful attention is given to recording pulse and blood pressure and de-

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termining their product at the time of angina, no clear pattern may be noted to account for the occurrence of pain.[7]

Role of coronary vasospasm: These observations invite the concept of variation in dimension of the coronary luminal delivery system that may at times respond to other than hemodynamic factors and induce profound myocardial consequences. The most attractive mechanism for altering flow is coronary vasospasm. But is this limited merely to the small subset afflicted with Prinzmetal's variant angina, or does it also operate in classic Heberden's angina? Are such transient luminal changes progenitors in the chain of events that lead to myocardial infarction? How frequently does coronary arterial spasm become a factor predisposing to sudden cardiac death?

Sometimes individual clinical observations may illuminate a wide terrain. The following two patient experiences noted more than 25 years ago are still worthy of recall. In the first case, a 40 year old man who had far advanced coronary artery disease, consistently experienced anginal pain and exhibited marked S-T segment depression after 44 crossings during a Master two-step test.[8] Week after week when he was retested at the count of 40, he began to note chest tightness that by the 44th crossing was of a severity compelling him to stop. This was curious because of its consistency and utter lack of relation to heart rate and blood pressure, although each time he exhibited 2 to 3 mm S-T segment depression and a third sound gallop. When thereafter the count was conducted quietly but miscounted out loud to 40 when there had been only 28 passages across the two-step, he seemed startled but promptly began to complain of chest tightness and was forced to stop at the count of 44 after completion of only 32 crossings. On three further occasions, this result was replicated with concomitant development of significant objective changes of myocardial ischemia. Yet on two other occasions when the count was out loud and exercise was halted at 32 crossings, neither chest pain nor S-T segment deviations occurred. The most logical explanation is that the verbally conditioned Heberden's angina was caused by neurally or neurohumorally provoked coronary arterial vasospasm.

The second clinical experience relates to the mechanisms at the very onset of myocardial infarction. The patient, a 52 year old man, while waiting to be seen in cardiac consultation, noted the abrupt onset of severe and even excruciating chest pain, profuse sweating and nausea. Right carotid sinus pressure for a period of 15 minutes alleviated all symptoms and abolished the current of injury for the duration of this maneuver (Fig. 1). Carotid sinus pressure was not accompanied by a slowing of heart rate or a reduction in blood pressure. When carotid massage was discontinued, there was an immediate recurrence of symptoms and S-T segment elevation in leads II and III. The patient sustained an inferior myocardial infarction. Since this experience, the troubling question has recurred: How frequently is potentially reversible coronary vascular spasm the precipitant or the initial event in acute myocardial infarction?

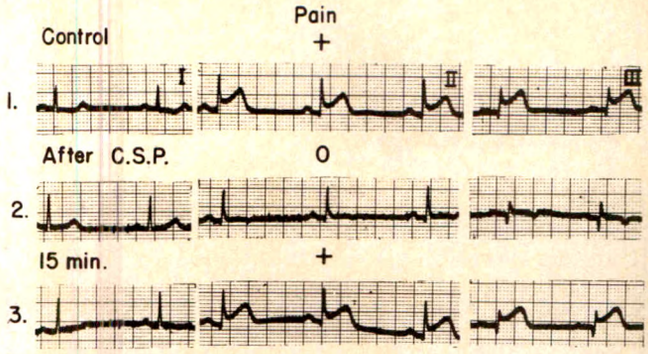

FIGURE 1. Panel 1, at the very onset of severe chest pain, a current of injury emerges in leads II and III. **Panel 2,** the pain is completely abolished, and the S-T segment elevation returns to baseline for the 15 minutes of the carotid sinus pressure (CSP). **Panel 3,** the pain and current of injury recur when the carotid maneuver is halted.

The question of coronary spasm also looms in relation to the massive problem of sudden cardiac death. With increasing electrocardiographic monitoring experience, one can observe at times the onset of malignant ventricular arrhythmias without prodromal ectopic activity. This phenomenon is analagous to the findings in animals after coronary reperfusion.[9] The tendency to ventricular fibrillation after occlusion of a major coronary artery in the dog is less than after release of the occlusion with reperfusion. In patients with Prinzmetal's angina it is now widely appreciated that a current of injury and ventricular arrhythmia can occur without pain. It may well be that painless spasm infringing on blood flow sets the stage for the release of some myocardial metabolites resulting from ischemia, that on reperfusion after cessation of spasm, cause electric instability leading to sudden death.

The role of vasospasm as a cause of diverse manifestation of coronary artery disease is now on the agenda of early scientific resolution. The present Symposium largely addresses this issue and deals with four interrelated topics: (1) the intimate subcellular mechanisms by which calcium flux affects smooth muscle contraction; (2) the role of coronary spasm in ischemic heart disease; (3) the action of nifedipine in various syndromes of ischemic heart disease; and (4) the protective effect of nifedipine on the variously jeopardized myocardium. Frequently, a new drug not only affords a remedy for a specific symptom but provides a research tool to probe the underlying maladaptive physiologic and biochemical processes. It is to be hoped that the calcium flux inhibitors will permit the breaking of new ground not only for the alleviation of angina pectoris but, of more importance, also in the prevention of the deleterious sequelae of ischemic heart disease.

Acknowledgment

The contribution of Dr. Jerome Weinstein in organizing this Symposium is gratefully acknowledged.

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Role of Calcium and Cyclic Adenosine 3′:5′ Monophosphate In Regulating Smooth Muscle Contraction

Mechanisms of Excitation-Contraction Coupling in Smooth Muscle

ROBERT S. ADELSTEIN, MD
DAVID R. HATHAWAY, MD

Bethesda, Maryland

Calcium initiates smooth muscle contraction by activating an enzyme, myosin light chain kinase. This enzyme catalyzes the transfer of phosphate from adenosine triphosphate to the 20,000 dalton light chain of myosin. In its phosphorylated form myosin interacts with actin to produce muscle contraction. The mechanism by which calcium activates myosin kinase requires (1) the binding of calcium to a 16,500 dalton calcium-binding protein (calmodulin), and (2) the binding of calmodulin-calcium to a 125,000 dalton catalytic subunit. This two protein complex is the active form of myosin light chain kinase.

Smooth muscle relaxation is mediated by cyclic adenosine 3′:5′ monophosphate (cyclic AMP). One mechanism by which the latter may exert a direct effect on actin-myosin interaction is through the activation of a cyclic AMP-dependent protein kinase that can phosphorylate the 125,000 dalton component of myosin light chain kinase. Phosphorylation of myosin light chain kinase decreases the activity of the enzyme, thus favoring the unphosphorylated form of myosin, which cannot interact with actin to produce smooth muscle contraction.

Contraction of smooth, cardiac and skeletal muscle requires the interaction of the contractile proteins actin and myosin. Actin and myosin from smooth muscle resemble their counterparts from striated muscle in their general molecular configuration. However, there is a major difference between the mechanisms by which calcium regulates actin-myosin interaction in smooth and striated muscle.

Adenosine 3′:5′ monophosphate (cyclic AMP) is thought to play an important role in mediating the effects of hormones and pharmacologic agents on muscle contraction and relaxation. Until recently, the mechanism by which cyclic AMP might have a direct effect on smooth muscle contraction was unknown. The purpose of this article is to review recent information on one mechanism by which calcium and cyclic AMP may regulate the interaction of smooth muscle actin and myosin.

The Contractile Proteins

Actin: Smooth muscle actin is a globular protein with a molecular weight of 42,000. In the contractile apparatus actin exists as long filaments composed of double-stranded helical polymers of globular subunits (Fig. 1). In its filamentous form actin is associated with a fibrous protein, tropomyosin, which has a molecular weight of 66,000 and is composed of two subunits. Tropomyosin molecules align themselves end to end in the groove of the actin helix (Fig. 1). At present no specific function has been assigned to tropomyosin in smooth muscle, although in striated muscle (see later) it acts with troponin to mediate calcium regulation of the actin-myosin interaction.

From the Section on Molecular Cardiology, Cardiology Branch, National Heart, Lung, and Blood Institute, Bethesda, Maryland. Manuscript received April 4, 1979; revised manuscript received July 31, 1979, accepted August 1, 1979.

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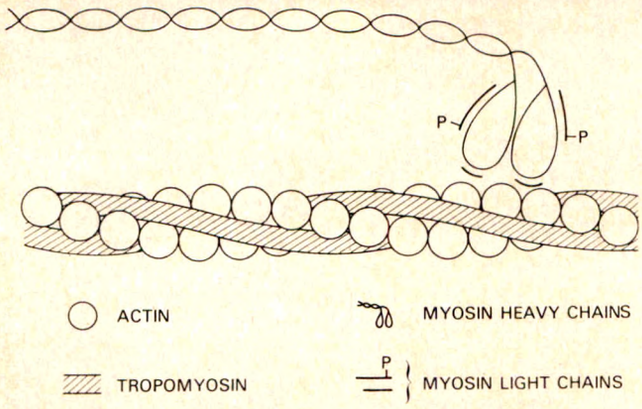

FIGURE 1. Diagrammatic representation of three contractile proteins found in muscle cells. Myosin has a molecular weight of 460,000. The globular region of the molecule contains the actin-binding sites and the sites of adenosine triphosphatase activity. The precise location of the myosin light chains is not known. Actin is a polymer of 42,000 dalton monomers, which polymerize to form a double-stranded helix. The exact function of tropomyosin in smooth muscle cells is unknown. In skeletal and cardiac muscle it acts together with troponin (not shown) to make the interaction of actin and myosin dependent on the presence of calcium. P = phosphate. (Reprinted by permission, from Adelstein.[1])

Myosin: Smooth muscle myosin has a molecular weight of 460,000 and is composed of three pairs of polypeptide chains: one pair of heavy chains with molecular weights of 200,000 and two pairs of light chains with molecular weights of 20,000 and 15,000 (Fig. 1). In muscle cells the individual myosin molecules are aligned into filaments arranged so that a portion of the molecule (called the head) extends toward the actin filaments and is available for interaction.

Besides being a major structural protein, myosin is also an enzyme that catalyzes the hydrolysis of adenosine triphosphate to adenosine diphosphate and inorganic phosphate with the liberation of heat and energy. In the absence of actin, this hydrolysis proceeds very slowly, but in the presence of actin, under conditions described later, the hydrolysis of adenosine triphosphate increases 100-fold. Two important features of this interaction are as follows: (1) The energy liberated is used to slide actin filaments along myosin filaments, thereby generating tension or movement; and (2) calcium is required to initiate the interaction of actin and myosin in smooth and striated muscle, although by different mechanisms.

The hydrolysis of adenosine triphosphate (ATP) by myosin: This can be quantitated in vitro by measuring the rate at which inorganic phosphate is released as ATP is broken down to adenosine diphosphate and inorganic phosphate. A high rate of ATP hydrolysis (for example, 200 nmole of inorganic phosphate liberated per milligram of myosin per minute) by smooth muscle myosin in the presence of actin, which is termed actin-activation of myosin adenosine triphosphatase activity, is the "test tube" equivalent of contraction. A low rate of hydrolysis (2 to 3 nmole of inorganic phosphate released per milligram per minute) in the presence of these two proteins is the equivalent of relaxation.

A fundamental difference between striated and smooth muscle myosins is that smooth muscle myosin requires a modification of one pair of its light chains, the 20,000 dalton light chain, in order for actin-activation of myosin adenosine triphosphatase activity to occur.[1] This modification, which is under enzymatic control, consists of the addition of phosphate (donated by ATP) to a particular serine residue on the myosin molecule. Myosin phosphorylation is a prerequisite for actin-activation of smooth muscle myosin adenosine triphosphatase activity[2–4] and, hence, for contraction (Fig. 2).

Phosphorylation of myosin: Because contraction-relaxation is a cyclical phenomenon, one might expect this property to be reflected in the phosphorylation reaction. As shown in Figure 2, this is in fact the case. Phosphorylation of myosin is catalyzed by a specific enzyme, myosin light chain kinase, and the reverse reaction, which restores myosin to its unphosphorylated form, is controlled by the enzyme myosin light chain phosphatase.[3,5]

The Role of Calcium

Regulation of actin-myosin interaction by calcium: The myosins from skeletal and cardiac muscle do not require light chain phosphorylation as a prerequisite for interaction with actin. When actin is added to purified myosin from striated muscle, activation of myosin

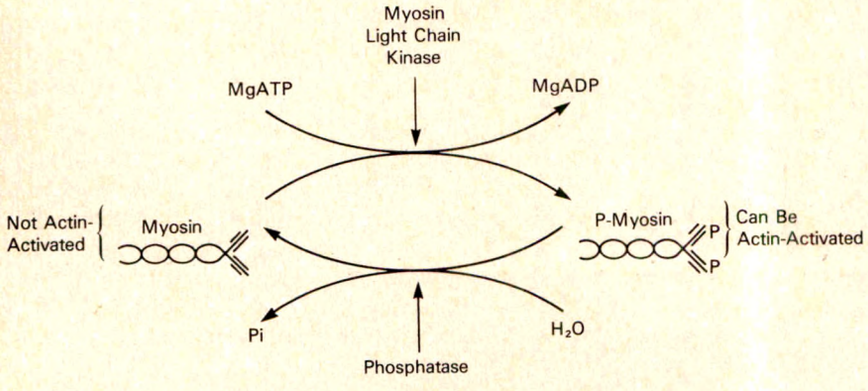

FIGURE 2. Control and effect of myosin phosphorylation. Diagram of the myosin molecule illustrates the heavy chains, which are coiled about each other in the rod portion of the molecule, and the two sets of light chains. The larger light chain (20,000 daltons) is phosphorylated (P). MgADP = magnesium adenosine diphosphate; MgATP = magnesium adenosine triphosphate; Pi = inorganic phosphate. (Reprinted by permission, from Adelstein and Pollard.[20])

adenosine triphosphatase occurs and ATP is rapidly hydrolyzed. In the native state, however, actin-myosin interactions is regulated by a mechanism that involves calcium. The actins from cardiac and skeletal muscle are associated with tropomyosin, which, as mentioned previously, lies in the groove of the actin helix. In this position, tropomyosin is associated with troponin, a three protein complex that in the absence of calcium inhibits the interaction of actin with myosin. The three proteins that constitute troponin are troponin T (for tropomyosin-binding), troponin I (for inhibitory) and troponin C (for calcium-binding). When intracellular calcium levels rise from a basal level of about 10^{-8} molar to levels associated with activation (about 10^{-6} molar), binding of calcium to troponin C results in a rearrangement of the troponin-tropomyosin complex so that actin can interact with myosin.

In smooth muscle, where myosin phosphorylation is required for interaction with actin, calcium initiates contraction by activating the enzyme myosin light chain kinase (Fig. 2).[6] The mechanism by which calcium regulates smooth muscle myosin kinase has recently been defined[7]; it requires the interaction of two proteins, one with a molecular weight[8] of 125,000 and a smaller protein of 16,500 daltons. Whereas the larger protein governs the specificity and unique ability of the enzyme to catalyze the transfer of phosphate from ATP to myosin, the smaller protein, named calmodulin, mediates the effect of calcium.

Calmodulin: This is a heat-stable calcium-binding protein, similar in chemical structure to troponin C, the calcium-binding subunit of troponin. It is widely distributed throughout the animal and plant kingdom and its amino acid sequence is markedly conserved. Calmodulin has been shown to bind to and activate various enzymes, but only in the presence of calcium.[7–13]

In smooth muscle, when the intracellular calcium level is 10^{-8} molar or less, calmodulin may not bind to the myosin light chain kinase, and the enzyme is inactive. When calcium levels rise to 10^{-6} molar, the following sequence is initiated: (1) Calcium binds to calmodulin; (2) the calcium-calmodulin complex binds to myosin kinase, resulting in activation of the enzyme; (3) the activated enzyme phosphorylates the 20,000 dalton light chain of myosin; and, finally, (4) actin and myosin interact to produce contraction. When the calcium concentration is lowered to resting levels, calmodulin dissociates from myosin kinase and myosin phosphorylation ceases. Because myosin light chain phosphatase (Fig. 2), unlike the kinase, is not regulated by calcium (or calmodulin), dephosphorylation of myosin occurs, and relaxation ensues.

Role for Cyclic Adenosine 3′:5′ Monophosphate

Regulation of intracellular calcium levels: An important role in smooth muscle relaxation is played by cyclic adenosine 3′:5′ monophosphate (cyclic AMP). Some investigations have focused attention on regulation of intracellular calcium levels by a cyclic AMP-mediated process. Studies with various preparations of smooth muscle have suggested that cyclic AMP may enhance calcium uptake by membrane fractions, accelerate calcium efflux from smooth muscle cells and prevent transmembrane influx of calcium.[14] In the typical scheme, agents that relax smooth muscle by a cyclic AMP-mediated mechanism share in common the ability to increase intracellular levels of cyclic AMP by stimulating adenylate cyclase, the enzyme that converts ATP to cyclic AMP, or by inhibiting phosphodiesterase, which degrades cyclic AMP to its inactive form, 5′ adenosine monophosphate. The principal effect of cyclic AMP is to activate a cyclic AMP-dependent protein kinase that can transfer phosphate from ATP to selected proteins directly involved in the regulation of intracellular calcium levels and in the interaction of actin with myosin. Thus, myosin light chain kinase, which regulates phosphorylation of myosin, can itself be phosphorylated by another kinase, regulated by cyclic AMP.

The catalytic subunit of cyclic AMP-dependent protein kinase catalyzes the incorporation of 1 mole of phosphate per mole of myosin light chain kinase.[8] Phosphorylation of myosin light chain kinase results in a two- to threefold *decrease* in the activity of this enzyme (Fig. 3).[8] The diminished activity of the phosphorylated myosin kinase appears to result from the inability of the phosphorylated enzyme to bind calmodulin as tightly as the unphosphorylated kinase (Conti and Adelstein, unpublished observations).

Inhibition of myosin light chain kinase activity: The scheme in Figure 4 shows how cyclic AMP may relax smooth muscle by inhibiting myosin light chain kinase activity. The mechanism of this inhibition can be described by following the cascade of molecular events that occur when intracellular levels of cyclic AMP rise. Catecholamines, for example, bind to beta adrenergic receptors, stimulating adenylate cyclase to convert adenosine triphosphate to cyclic AMP. The

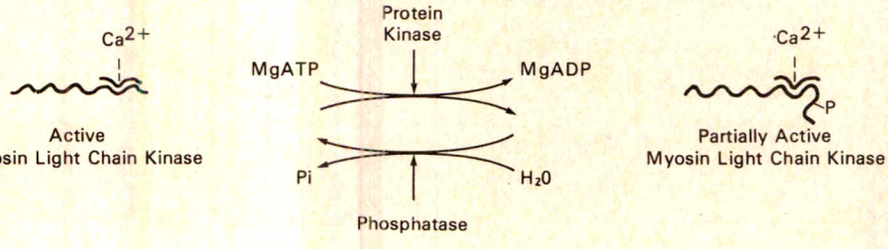

FIGURE 3. Diagram illustrating the phosphorylation and resultant decrease in activity of myosin light chain kinase by the catalytic subunit of cyclic adenosine 3′:5′-monophosphate (cyclic AMP). Abbreviations as in Figure 2.

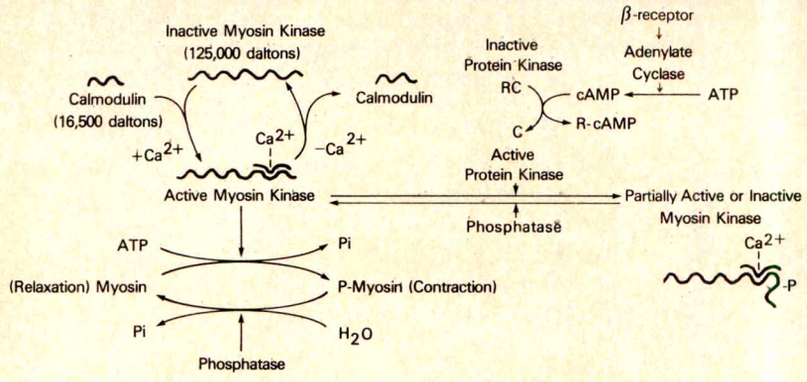

FIGURE 4. Schematic representation of one mechanism by which calcium and cyclic adenosine 3′:5′ monophosphate regulate smooth muscle contraction. Calcium binds to calmodulin (16,500 daltons), which permits binding of calmodulin to myosin light chain kinase. The active calmodulin-myosin kinase complex phosphorylates myosin, which results in contraction (P-myosin). Dephosphorylation of myosin by a phosphatase promotes relaxation. Cyclic adenosine 3′:5′-monophosphate cAMP is synthesized from adenosine triphosphate (ATP) by the enzyme, adenylate cyclase, which is coupled to specific receptors on the outer smooth muscle cell membrane (that is, the beta adrenergic receptor). cAMP activates protein kinase by liberating a catalytic subunit (C), which can phosphorylate myosin kinase. The phosphorylated myosin kinase is only partially active in vitro and may be inactive in vivo. The net effect of this sequence is to inhibit phosphorylation of myosin, thus favoring relaxation. R = regulatory subunit of protein kinase.

latter, in turn, activates protein kinase by binding to the regulatory subunit of this enzyme, liberating the catalytic subunit. The free catalytic subunit can then catalyze the phosphorylation of myosin light chain kinase. Whereas our in vitro experiments have demonstrated that phosphorylation of myosin kinase markedly diminishes its activity, it is possible that in vivo the enzyme is rendered completely inactive by phosphorylation. However, whether the inhibition of myosin kinase activity is partial or complete, the net effect of phosphorylating myosin light chain kinase is to prevent phosphorylation of the 20,000 dalton light chain of myosin. Because unphosphorylated myosin cannot interact with actin, smooth muscle relaxation ensues.

Conclusions

In this review we have discussed some of the recent information on how calcium and cyclic nucleotides can act to regulate smooth muscle contraction. Calcium plays a central role because it is required for activation of myosin light chain kinase. The active kinase catalyzes the phosphorylation of myosin, which can then interact with actin to effect contraction (Fig. 4). To date, most of the information about this mechanism has come from in vitro experiments; these observations need to be substantiated in vivo. The importance of myosin phosphorylation in generating smooth muscle tension has recently been documented in skinned smooth muscle fibers.[15]

Regulation of smooth muscle contraction by phosphorylation does not preclude the existence of other regulatory mechanisms, which may also involve calcium. To date, no firm evidence has been presented to indicate the presence of troponin in smooth muscle. However, Ebashi et al.[16] recently described a regulatory mechanism based on two novel smooth muscle proteins. The importance of this second form of regulation is still to be determined.

Recent evidence has documented the importance of myosin phosphorylation in a wide variety of smooth muscle tissues, including those of the gizzard,[2,4,5] vas deferens,[3] arterial wall,[17] stomach,[6] uterus[18] and placenta.[19] It will be of interest to learn whether all these systems are regulated in exactly the same manner or whether, as appears likely, there are subtle differences in how calcium and cyclic nucleotides regulate contraction-relaxation in these different tissues.

Acknowledgment

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Significance of Spasm in the Pathogenesis of Ischemic Heart Disease

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The role of coronary arterial vasospasm in the pathogenesis of ischemic heart disease is reviewed on the basis of investigations carried out in our laboratory. Patients were selected because they had angina either at rest or both at rest and during exercise. With continuous hemodynamic and electrocardiographic monitoring of these patients, as well as thallium-201 scintigraphy and coronary arteriography during ischemic episodes, we were able to demonstrate a vasospastic origin for the attacks. During anginal episodes, electrocardiographic changes were variable, with S-T segment elevation, S-T segment depression, a rise in T wave potential and pseudonormalization of inverted T waves corresponding to various distributions of myocardial ischemia in different patients and even in the same patient at different times. Increases in hemodynamic variables that control myocardial oxygen consumption never preceded the onset of ischemic episodes, which challenges the theory that the limitation of a possible increase in flow caused by critical organic stenosis is the only cause of myocardial ischemia. In some patients in whom myocardial infarction developed, the lesion was always found in the same area in which the vasospastic phenomena had been seen angiographically. Vasospasm led to serious arrhythmias in some patients. We therefore believe that independent of atherosclerosis or superimposed on it, vasospasm plays an important role in producing myocardial ischemia—angina, myocardial infarction and possibly sudden death. Elucidation of its mechanisms will lead to more appropriate therapy.

Coronary vasospasm is increasingly being recognized as a cause of variant angina[1–15] and myocardial infarction.[16–24] Although Heberden[25] postulated its existence as early as 1768, and others[26–28] echoed his belief from time to time, coronary arterial spasm was until recently presumed not to exist because techniques to demonstrate its presence were unavailable.

The field of ischemic heart disease is now undergoing a transition similar to the one that followed the introduction of cardiac catheterization and angiography to the field of congenital heart disease. It was then discovered that blue babies were not the only casualties of congenital heart disease but that many other congenital defects were responsible for the same clinical manifestations. Similarly, ischemic heart disease is emerging as a condition having multiple causes, one of which is coronary arterial spasm.

Problems in Ischemic Heart Disease

It might be well to broaden our field of vision and put into perspective some of the general problems we face in relation to ischemic heart disease. Traditionally, coronary atherosclerosis has been the common ground for the clinical manifestations of ischemic heart disease including angina pectoris, sudden death and myocardial infarction. However, new technology and new interest and unbiased approaches to the study of these clinical manifestations are making it increasingly clear that the relation between atherosclerosis and the symptoms of ischemic disease

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is not a linear one. The following data illustrate the point:

(1) Only 1 in 10 persons with coronary atherosclerosis is symptomatic. (2) The severity of symptoms correlates poorly with the severity of coronary atherosclerosis. Some patients have severe atherosclerosis with mild symptoms whereas others have minimal atherosclerotic lesions with severe clinical symptoms. (3) Approximately 10 percent of patients with angina pectoris or myocardial infarction have normal or nearly normal coronary arteries. (4) The severity of coronary atherosclerosis is often similar in patients with either stable or unstable angina even though unstable angina carries a much greater risk of complications including infarction and sudden death.

On the basis of these incongruities, we began in 1973 to approach the problem by studying essentially the one manifestation of ischemic heart disease that best lends itself to systematic investigation: angina pectoris. Myocardial infarction and sudden death were discarded as subjects of study because they can only be observed after they occur, and there is little possibility that their cause will be seen. We further elected to study the subgroup of patients with angina at rest, that is, unstable angina, because they usually have frequent anginal attacks and can therefore be observed more readily.

Prinzmetal et al.[29] in 1959 called attention to a variant form of angina characterized by dramatic changes in the electrocardiogram consisting of S-T segment elevation instead of the classic S-T segment depression. S-T segment elevation indicated an acute transmural ischemia not altogether unlike that of myocardial infarction and, in fact, many of these patients later had a myocardial infarction.[30]

Determining the Role of Coronary Vasospasm

Hemodynamic studies: A first series of studies with hemodynamic monitoring undertaken at our laboratory[31] showed that there was no increase in myocardial oxygen consumption preceding, thus causing, the ischemic attacks in patients with variant angina. Instead, the ischemia was due to coronary arterial spasm, which was demonstrated angiographically.[32] At that time, however, our findings were questioned on the basis that angiographically demonstrated coronary spasm may be catheter-induced.

Thallium imaging: To resolve this doubt, we performed a second series of studies in similar patients with variant angina.[33] Using myocardial thallium scintigraphy, we demonstrated that these attacks were caused by massive transmural deficits in myocardial perfusion. These deficits correlated well with the regions from which S-T segment elevations had been recorded during episodes of pain and also corresponded with the vascular territory shown angiographically to have undergone vasospasm during similar attacks.

Confirmation of these findings came from several studies[4,6,7,15,17,18,21,22] within a relatively short time, and an editorial[1] stated that the hypothesis of coronary spasm as the cause of Prinzmetal's angina could be considered proved. However, it remained to determine what Prinzmetal's angina really was, how frequently it occurred and what the problems were with other types of angina.

What Is Variant Angina?

Alternate S-T segment elevation and depression: In studies carried out in 1974 and 1975, we came across some patients whose signs and symptoms represented transitional forms between variant and ordinary angina. They exhibited S-T segment elevation but at times also displayed S-T segment depression within minutes, hours or days or in an alternating fashion.

Hemodynamic changes: When these patients were monitored hemodynamically, they might at first have an episode characterized by S-T segment elevation (Fig. 1, left). Yet before the episode there were no increases in factors determining oxygen demand such as heart rate, first derivative of left ventricular pressure (dP/dt) or systolic pressure; only during the episode were an increase in heart rate, a decrease in systolic pressure, an increase in end-diastolic pressure and a decrease in dP/dt noted; everything would then return to normal. Minutes or hours later (Fig. 1, right), a second episode might occur, characterized by S-T segment depression with either positive or negative T waves. The same lack of hemodynamic changes was found before the second episode as before the first, and the same changes occurred during the second episode as during the first, but they were of slighter degree. These findings were repeatedly confirmed by careful objective analysis of hemodynamic variables by computer.

On the basis of these studies, we concluded that variant angina is only one extreme in a continuous spectrum of vasospastic myocardial ischemia,[34] because we had earlier observed that vasospasm could also occur in association with S-T segment depression.[3] Prolonged vasospasm can lead to myocardial infarction and sometimes result in a fatal ventricular arrhythmia, as will be discussed subsequently.

How Frequent Is Vasospasm?

In our experience vasospasm is more frequent than heretofore believed. The results of continuous hemodynamic and electrocardiographic monitoring, which allowed us to record some 8,000 to 9,000 episodes of transient acute myocardial ischemia, bear this out. The onset of pain is usually *followed, and by minutes,* by electrocardiographic changes. Many transient episodes of S-T segment elevation, S-T segment depression or T wave changes are asymptomatic; that is, the patient has no chest pain. In some patients, a majority and in some only a few ischemic episodes are asymptomatic. The extent and duration of the S-T segment and T wave changes often vary in the same patient in successive ischemic episodes and even during the same episode. Throughout our studies we could not find any difference in the hemodynamic changes during symptomatic or asymptomatic episodes or in the incidence of potentially fatal arrhythmias, which can also occur without chest pain but with only electrocardiographic changes.

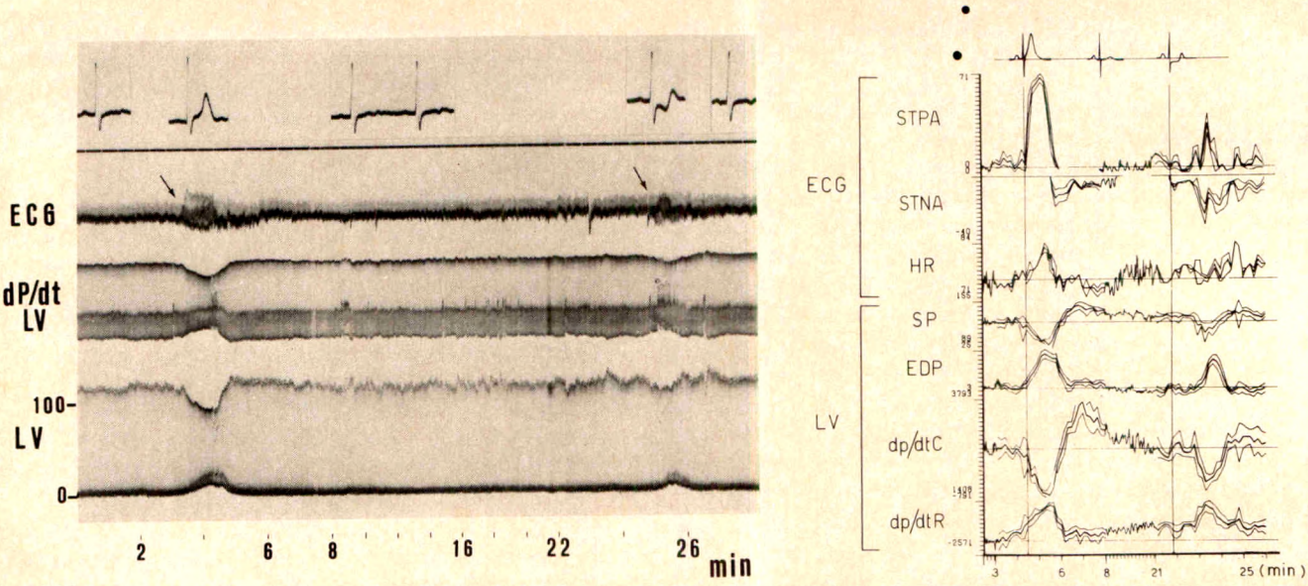

FIGURE 1. Continuous playback of hemodynamic recording, performed in a patient who had anginal episodes with both S-T segment elevation and depression, on photographic paper (**left**) and analyzed by computer (**right**). The recording demonstrates that transient episodes of acute myocardial ischemia with S-T segment elevation and depression may occur in the same leads within a few minutes, without symptoms. During the recording, the patient had several anginal episodes with variable electrocardiographic changes; some episodes were asymptomatic. Here are illustrated two successive asymptomatic episodes characterized by hemodynamic changes similar to those observed during symptomatic episodes. **Left,** the onset of the changes is indicated by **arrows**. **Right,** the onset of the episodes of S-T segment elevation and depression (**vertical lines**) is not preceded by an increase in heart rate (HR), systolic blood pressure (SP) or contractility. These electrocardiographic changes are associated with impairment of first derivative of left ventricular pressure (dP/dt) with an increase in diastolic and a reduction in systolic pressure of the left ventricle (LV). dp/dt C and R = peak contraction and relaxation dP/dt; EDP = end-diastolic pressure; STPA and STNA = positive and negative areas of the S-T segment of the electrocardiogram.

In all patients studied, thallium scintigraphy showed a regional decrease in myocardial perfusion. The decrease was massive during episodes of S-T segment elevation or pseudonormalization of negative T waves, probably reflecting transmural ischemia. However, the underperfusion was diffused, with fuzzy limits, during episodes of S-T segment depression, which probably indicated subendocardial ischemia. In either case, a reduction in coronary blood supply appeared to be the direct cause of angina, independent of the direction of S-T changes. Furthermore, coronary spasm can involve vessels with a variable degree of atherosclerosis. The spasm usually involves a long segment of the vessel and can be either proximal or distal to an organic lesion. It may also involve to a variable extent more than one vessel. Therefore, the traditional concept of increased myocardial oxygen demand as the cause of angina did not appear to be valid for these patients with spontaneous attacks of angina at rest.

Stress Testing

Initially, we were wary of performing tests in patients with angina at rest. However, as our experience increased, we found that we could perform these tests after carefully excluding those patients whose exercise tolerance was obviously very low. We also found that the tests were important in evaluating these patients. About 10 percent of the patients tested had normal submaximal stress results; the remainder had positive test results, and their heart rate-systolic blood pressure product was much higher than at the onset of S-T segment changes at rest. In some patients, the signs of ischemia appearing in the electrocardiographic leads during stress testing differed from the usual ones during angina at rest (Fig. 2). The patients were having the same symptoms, that is, pain at rest and during exercise, but the ischemia was apparently occurring in different regions of the heart, probably as a result of different pathogenic mechanisms.

Vasospasm, Myocardial Infarction and Exertional Angina

From our observations, particularly at arteriography, we hypothesize that repeated prolonged vasospasm may cause blockage of vessels and stagnation of blood, with possible damage to the intima,[35] plaque buildup or hemorrhage or rupture, associated with platelet aggregation and thromboxane A_2 release.[36] This could initiate a vicious circle that could produce thrombosis, increased vasoconstriction, or both, with prolonged ischemia leading to myocardial infarction.[30] We have seen that vasospasm can play a role in when the patient has angina at rest and also when the patient has severe coronary atherosclerosis and is exercise-limited by exertional angina. Therefore, spasm may well play a role in the more common types of angina, because the two forms of angina, angina at rest and exertional angina, can exist in a single person.

Vasospasm and Sudden Death

Sudden death can occur in a person with normal coronary arteries. In our studies, when we continuously

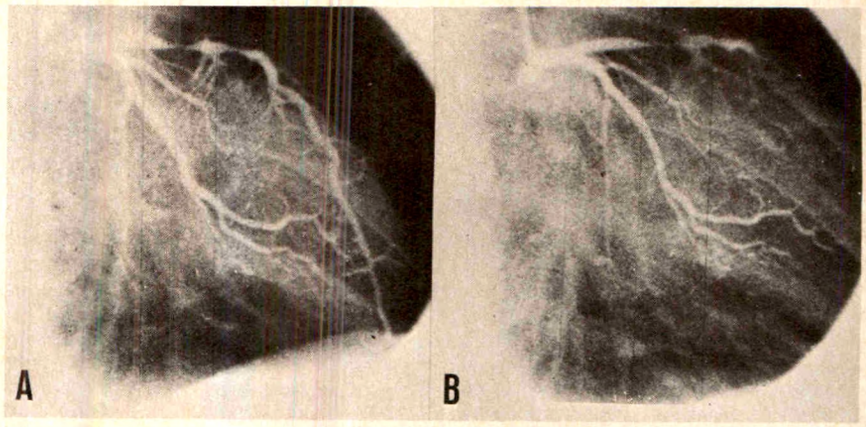

FIGURE 2. Left coronary angiograms in a 60 year old man with typical effort angina and positive electrocardiographic exercise test. **A,** angiogram in the absence of symptoms, showing two severe atherosclerotic obstructions in the proximal third of the left anterior descending coronary artery; and **B,** angiogram during a spontaneous episode of angina at rest showing complete occlusion distal to the second stenosis with no distal filling. Thus, the patient had both typical angina during exertion and angina at rest caused by vasospasm.

monitored some patients with S-T segment elevation, we found that during resolution of the attacks the patients often exhibited deep negative T waves (Fig. 3). On further examination of this period of negative T waves, we found incomplete spasm with late filling of the distal branch, which was completely occluded during S-T elevation. Thus, a partial reflow phenomenon was taking place. During the period of negative T waves, these patients usually showed ventricular tachycardia, which sometimes led to ventricular fibrillation. The only way we could prevent these episodes of fibrillation was by treating the symptom, that is, by treating the angina rather than by administering antiarrhythmic drugs. Preventing angina meant preventing ventricular fibrillation in these cases.

Conclusions

Until more is known about the manifestations of myocardial ischemia, we can temporarily state as a working hypothesis that coronary atherosclerosis leads, through modulatory factors, to myocardial ischemia, which in turn is responsible for the clinical manifestations of the disease. However, we also know now that myocardial ischemia can occur with little or no atherosclerosis. Therefore, our attack on the problem in terms of therapy and prevention should be directed not only to treating coronary atherosclerosis but also to identifying the modulatory factors responsible for the appearance of symptoms. We need to know what is causing coronary spasm and whether other causes, besides spasm, can produce angina or acute myocardial ischemia. Such other causes are likely to exist, but we must look for them if they are to be found.

The present problem lies in identifying the causes that lead to acute myocardial ischemia independent of the degree of coronary atherosclerosis or of increased myocardial oxygen demand. Identification of such causes will profoundly influence our everyday approach to therapy and also the future direction of research.

Therapeutic Implications

A better understanding of the causes of myocardial ischemia should lead to the development and use of appropriate pharmacologic therapy and to intervening measures to prevent the clinical manifestations of ischemic heart disease. Therapy for patients in whom spasm seems to be the main cause of myocardial ischemia is empiric and difficult to evaluate, because long-term study of these patients indicates that there is a natural waxing and waning of the disease. However, because spasm is known to occur in coronary artery smooth muscle, it is reasonable to use agents, such as nitrates, that prevent this excessive muscle contraction.[37] These agents are effective, and their dilating effect may be supplemented by some of their other actions such as afterload reduction. They have been shown to dilate coronary arteries even in stenotic areas. Calcium antagonists can also be used because they prevent smooth muscle contraction. These agents may be even more appropriate than nitrates for prolonged treatment

FIGURE 3. Asymptomatic myocardial ischemia associated with malignant dysrhythmia. The patient had reported a history of fainting during chest pain; ventricular fibrillation was repeatedly documented in the coronary care unit when S-T segment elevation was followed by deep negative T waves, with or without anginal pain. This low speed playback of an electrocardiogram (**above**) and an aortic pressure tracing (**below**) shows two transient episodes of ventricular fibrillation that spontaneously reverted to sinus rhythm at the end of an asymptomatic episode. Three years after these observations were made, the patient died suddenly at home during an anginal attack. He had a normal coronary arteriogram with documented occlusive spasm of the right coronary artery during S-T elevation in inferior leads followed by incomplete spasm during the period of negative T waves.

of these patients, because large dosages of nitrates may lead to tolerance or dependence. Verapamil and nifedipine, new and potent calcium antagonists, have been effective in suppressing spasm-induced angina.[38,39]

We use intravenous infusions of nitrates[40] and calcium antagonists in severely ill patients. In patients who are less severely ill and in those whose condition is improving, we taper the dosages of nitrates and reduce the dosage of calcium antagonists. Therapy must be individualized and the patients followed up closely. Some patients have been maintained on calcium antagonist therapy for up to 3 years.

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Inappropriate Coronary Vasoconstriction in Patients With Coronary Artery Disease: A Role for Nifedipine?

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Coronary arterial vasoconstriction, well recognized in Prinzmetal's variant angina, may participate in the pathogenesis of classic angina as well. Several recent studies in patients with obstructive coronary artery disease suggest that apparently spontaneous reductions in coronary blood flow can result in myocardial ischemia and even infarction. Evidence supporting the alpha adrenergic nervous system as a cause of such coronary vasoconstriction is reviewed, particularly the results of provocative testing with the cold pressor stimulus. Upon exposure of the skin to cold, patients with coronary artery disease demonstrate an inappropriate coronary vasoconstrictor response, often sufficient to produce angina. Normal patients, by contrast, show no change in coronary vascular resistance. In patients with a diseased coronary circulation, inappropriate vasoconstriction further restricts myocardial perfusion and appears to be little affected by beta adrenergic blocking agents or nitrates in the usual dosages. Nifedipine has proved effective in preventing coronary arterial spasm in patients with Prinzmetal's angina. Studies currently in progress suggest that it is also effective in blocking inappropriate coronary vasoconstriction in patients with typical angina. Nifedipine may thus be a useful addition to the treatment of ischemic heart disease.

A relation between spasm and angina pectoris has been suspected since 1768, when William Heberden, describing the disorder for the first time in a talk before the Royal Society of Medicine, concluded that the "spasmodic pains" of angina could be "justly attributed to the disturbed functions of the nerves."[1] In the 1870s, Latham[2] first implicated spasm of the coronary arteries as the cause of anginal attacks, a view that prevailed well into the 20th century. In 1910, for instance, Osler speculated that "there may be a perverted internal secretion that favours spasm of the (coronary) arteries."[3]

However, the subsequent demonstration of fixed, obstructive atherosclerotic lesions in most, if not all, patients with classic angina, coupled with the growing evidence for the close dependency of coronary blood flow on myocardial oxygen requirements,[4] gave rise to the now generally accepted view that angina results from an imbalance between a fixed, restricted myocardial oxygen supply and transiently increased metabolic demand. This concept is supported by the effectiveness in relieving angina of beta adrenergic antagonists and nitrates, agents that work primarily by reducing myocardial oxygen demand.

Role of Coronary Spasm in Classic Angina

The recent demonstration by arteriography that Prinzmetal's variant angina is caused by spasm of large coronary arteries[5–7] has renewed interest in the possibility that coronary vasospasm may also participate in the pathogenesis of classic angina.[8] Several lines of evidence suggest that a primary reduction in coronary blood flow, rather than enhanced metabolic demand, may in some instances precipitate angina pectoris

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and even myocardial infarction. Berndt et al.[9] found that during spontaneous attacks of angina in patients with obstructive coronary artery disease, the double product (heart rate × mean arterial pressure) and triple product (rate × pressure × left ventricular systolic ejection time) were not significantly different from those during pain-free periods, whereas during pacing-induced angina these products were markedly elevated. Because the double and triple products reflect the major determinants of myocardial oxygen consumption, these results suggest that a primary reduction in coronary flow was the cause of spontaneous angina in these patients.

Maseri et al.[10] presented data supporting a vasospastic origin of angina at rest in 76 patients with obstructive coronary artery disease studied during acute anginal attacks by hemodynamic monitoring, thallium-201 myocardial scintigraphy or coronary arteriography. In eight of these patients in whom myocardial infarction developed, the onset of infarction was indistinguishable from the onset of an attack of spontaneous angina. Oliva and Breckinridge[11] performed coronary arteriography in 15 patients within 12 hours of the onset of acute myocardial infarction. In six of these patients (40 percent) occluded coronary arteries could be opened by the intracoronary administration of nitroglycerin; this implicates coronary spasm in the pathogenesis of acute myocardial infarction.

While the existence of spontaneous coronary vasoconstriction in patients with obstructive coronary artery disease and classic angina thus seems clear, the causative mechanism for such vasoconstriction remains uncertain. One likely candidate is activation of the alpha adrenergic nervous system. Extensive experimental evidence in animals indicates that the normal coronary bed can respond to neural stimuli. Central sympathetic stimulation results in direct coronary vasoconstriction mediated by activation of alpha adrenergic receptors.[12,13] Withdrawal of tonic alpha adrenergic constrictor tone in conscious dogs by carotid sinus stimulation results in a marked decrease in coronary vascular resistance,[14] whereas in chloralose-anesthetized dogs activation of alpha constrictor tone by carotid sinus hypotension results in direct coronary vasoconstriction.[15] Such neurogenic vasoconstriction can effectively compete with metabolically induced vasodilatation, even in the presence of normal coronary arteries, which results in a widened myocardial arteriovenous oxygen difference and a decrease in coronary sinus oxygen content.[16]

Similar mechanisms may be operative in human beings as well. Heart transplant recipients respond to an intravenous infusion of the alpha blocking agent phentolamine with a significantly smaller decrease in coronary resistance than do patients with normally innervated hearts, which suggests the presence of tonic alpha adrenergic coronary vasoconstrictor tone in the normal heart.[17]

We have sought to determine whether increases in coronary vascular resistance due to activation of alpha adrenergic receptors might contribute to myocardial ischemia in patients with coronary artery disease.[18,19] Our results support the concept that coronary vasoconstriction may play a role in the pathogenesis of classic angina pectoris, and since they provide a framework for evaluating the usefulness of nifedipine, a potent coronary vasodilator in this disorder, our methods and results will be reviewed here.

Demonstration of Inappropriate Vasoconstriction in Patients with Coronary Artery Disease

Coronary vascular resistance was measured in 24 patients with stable chest pain syndromes before and during the initial 50 seconds of the cold pressor test,[18] a stimulus known to produce generalized vasoconstriction and a hypertensive response mediated by the alpha adrenergic receptors of the sympathetic nervous system. Accurate measurement of coronary resistance was made possible by the coronary sinus thermodilution method.[20] This technique permits continuous measurement of coronary sinus flow, which approximates 95 percent of coronary arterial flow.

During diagnostic cardiac catheterization, a thermodilution pacing catheter was placed in the coronary sinus through an antecubital vein. After the heart was paced to a subanginal rate of 95 beats/min, an indicator solution at room temperature (22° C) was injected through the thermodilution catheter at the rate of 39 ml/min. Baseline coronary sinus flow and arterial pressure were recorded simultaneously. A cold pressor stimulus followed; that is, the patient's right hand was immersed in ice water for 1 minute while coronary sinus flow and arterial pressure were continuously recorded. Coronary vascular resistance was calculated as the quotient of mean arterial pressure and coronary sinus flow during the control period and at 10 second intervals during the cold pressor test.

The cold pressor test evoked a similar hypertensive response in normal (control) subjects and in patients with coronary artery disease (Fig. 1, top). In both groups baseline mean arterial pressure rose by approximately 15 mm Hg. In the control subjects coronary sinus flow increased appropriately (Fig. 1, middle). Calculated coronary vascular resistance thus remained unchanged (Fig. 1, bottom).

In the group with coronary disease, however, coronary flow actually decreased, from a mean of 134 to 120 ml/min (Fig. 1, middle). Calculated coronary vascular resistance for this group increased during the entire cold pressor test and at peak pressor response averaged 27 percent above baseline values (Fig. 1, bottom). Angina developed in 5 of the 12 patients. Figure 2 illustrates the typical hemodynamic changes observed in one of these patients. Three patients in the group with coronary artery disease underwent another cold pressor test after the intravenous administration of 5 mg of phentolamine. The expected hypertensive response to the cold pressor stimulus failed to occur, and there were no changes in coronary sinus flow or coronary resistance.

Comparison of Metabolic and Vasoconstrictor Stimuli on Coronary Vascular Resistance

Effects of atrial pacing versus cold pressor test: The inappropriate coronary vasoconstriction observed

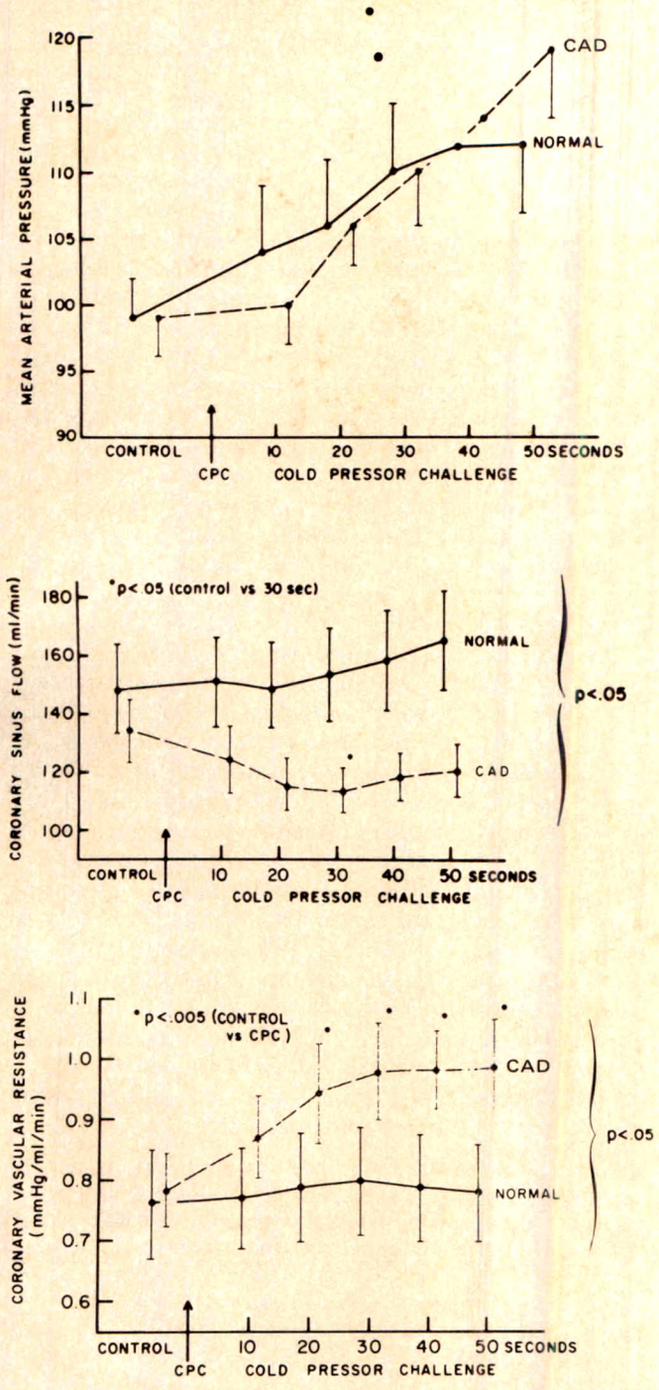

FIGURE 1. Effects of the cold pressor test in patients with normal coronary vessels (normal) and those with coronary artery disease (CAD). **Top,** in both, the hypertensive response was similar: baseline mean arterial pressures rose by approximately 15 mm Hg. **Arrow** indicates beginning of cold pressor test (CPC), followed by readings at 10 second intervals. **Bars** indicate mean ± standard deviation. **Middle,** coronary sinus flow, calculated during the control period and at 10 second intervals during the cold pressor test, shows significant differences between the two patient groups. Flow increased in normal patients after cold stress, but decreased in patients with coronary artery disease from a control value of 134 to 120 ml/min at 50 seconds. **Bottom,** coronary vascular resistance calculated as the ratio of mean arterial pressure/coronary sinus flow during the control period and at 10 second intervals during the cold pressor test. Again, significant differences were observed between patients with normal vessels, in whom the mean baseline value of 0.76 mm Hg/ml remained throughout the cold stress, and patients with coronary artery disease, whose coronary vascular resistance increased significantly. (Reprinted by permission, from Mudge et al.[18])

in patients with coronary artery disease may represent competition between metabolic vasodilatation and neurogenic vasoconstriction.[16] To evaluate further the interaction between vasodilatory reserve and alpha adrenergic-mediated vasoconstriction, we subsequently compared changes in coronary vascular resistance during the metabolic stress of atrial pacing and during the cold pressor test in 27 additional patients: 13 control subjects and 14 patients with obstructive coronary artery disease.[19] In this study each patient first underwent the cold pressor test as described earlier. After hemodynamic values returned to baseline levels, heart rate was increased by 20 beats/min every 2 minutes until angina or atrioventricular block occurred or a rate of 150 beats/min was reached.

During pacing, the double product of heart rate × mean arterial pressure increased 97 percent in control subjects and 108 percent in patients with coronary artery disease. In both groups, coronary sinus flow increased (125 ± 11 to 187 ± 18 ml/min for control subjects and 127 ± 11 to 205 ± 21 ml/min for patients with coronary artery disease) and coronary vascular resistance decreased (−36 percent for control subjects and −39 percent for patients with coronary disease). Thus, increased metabolic demand in patients with obstructive coronary artery disease could be met by an appropriate coronary vasodilatation. *During the cold pressor test,* a comparable hypertensive response and a similar increase in double product (+17 percent in control subjects, and +19 percent in patients with coronary artery disease) developed in both groups. But whereas the control subjects exhibited an appropriate increase in coronary sinus flow (149 ± 13 to 187 ± 19 ml/min) so that coronary resistance remained unchanged (−4.0 percent [difference not significant]), the patients with coronary artery disease again failed to show an increase in coronary sinus flow (151 ± 9 to 147 ± 11 ml/min). Coronary vascular resistance in these patients rose 24 percent during the cold pressor test. In three patients angina developed both with pacing and

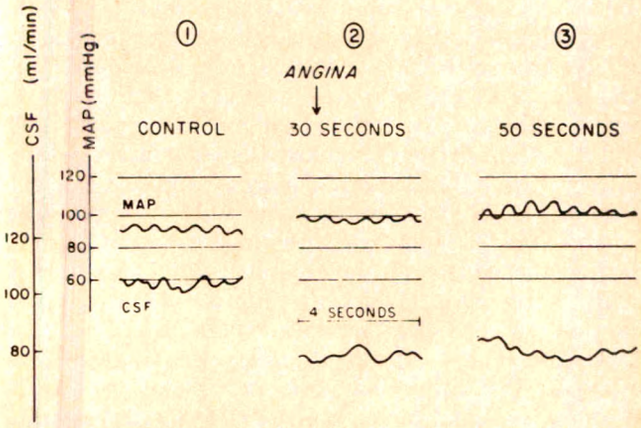

FIGURE 2. Response to the cold pressor test observed in a patient with coronary artery disease in whom angina developed in response to the cold stimulus. Although mean arterial pressure (MAP) increased, there was an actual reduction of coronary sinus flow (CSF), with the onset of angina at 30 seconds. (Reprinted by permission, from Mudge et al.[18])

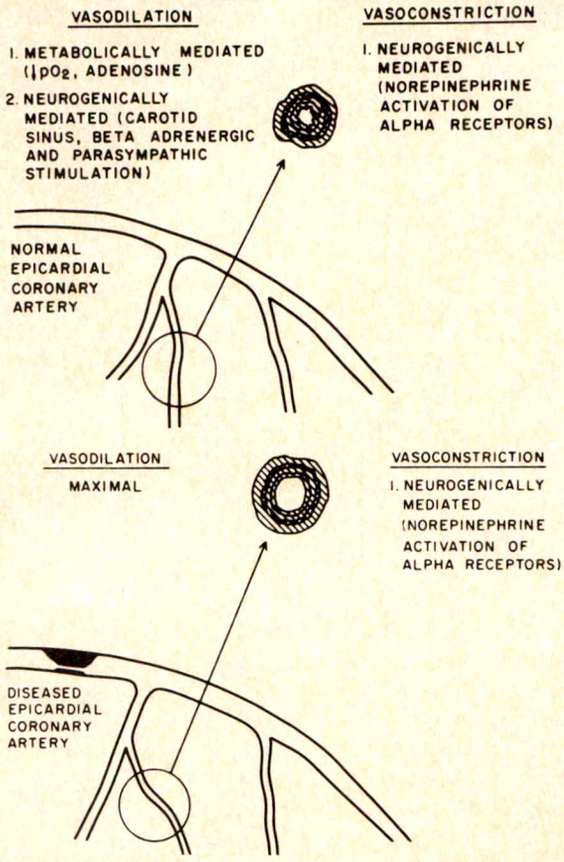

FIGURE 3. Vasodilatory and vasoconstrictive mechanisms potentially available in a normal (**top**) and diseased (**bottom**) coronary vascular bed. In the diseased coronary vessel, vasodilatation may be maximal and cannot increase to balance vasoconstrictor stimuli. (Reprinted by permission, from Mudge et al.[21])

during the cold pressor test. The double product during the cold pressor test was significantly lower in each patient than it was during pacing. This finding suggests that the ischemic pain in these patients occurred at a lower level of metabolic demand when provoked by a stimulus associated with vasoconstriction. In two patients whose left ventricular end-diastolic pressure was measured, diastolic compression of intramural vessels was excluded as a cause of the increased resistance.

Mechanism of increased coronary vascular resistance: The experimental results indicate that patients with coronary artery disease respond to the cold pressor stimulus in a manner that is fundamentally different from that of normal subjects and that worsens the basic problem of limited myocardial blood flow. We advance the following hypothesis to explain this unusual response[21]: In the normal coronary vascular bed (Fig. 3, top), any vasoconstrictor stimulus, such as the cold pressor test, can be effectively opposed by vasodilatation, either metabolically or neurogenically mediated. However, in the diseased coronary vascular bed (Fig. 3, bottom), vasodilatation is already maximal, to maintain resting flow at normal levels. Thereafter the vasoconstrictor stimulus is relatively unopposed, which results in an increased coronary vascular resistance, sufficient in many cases to produce myocardial ischemia.

Role of Nifedipine in Classic Angina

Therapy with the usual antianginal agents may not be effective in preventing myocardial ischemia produced by primary coronary vasoconstriction in patients with coronary artery disease. Beta adrenergic antagonists reduce myocardial oxygen consumption but theoretically could facilitate coronary vasoconstriction by inhibiting beta adrenergic vasodilatory effects. Nitrates apparently exert their effect primarily by means of changes in peripheral hemodynamics, that is, by reducing blood pressure and venous return. Doses sufficient to dilate coronary vessels directly may be accompanied by undue hypotension and reflex tachycardia, which may aggravate rather than relieve ischemia. The theoretical limitations of these drugs may apply in the clinical setting, because we have observed inappropriate vasoconstrictor responses even in patients on maintenance propranolol therapy who received sublingual nitroglycerin (up to 1.5 mg) immediately before the cold pressor test.

The ideal agent for preventing inappropriate coronary vasoconstriction in patients with coronary artery disease and classic angina would be a potent vasodilator with specificity for the coronary circulation, with little or no effect in clinical doses on systemic hemodynamics or myocardial contractility, thus preventing unwanted side effects. Nifedipine appears to be such an agent.[22] Clinical experience has shown it to be extremely effective in preventing the coronary spasm associated with Prinzmetal's angina, especially in cases refractory to standard modes of therapy.[23,24] Numerous studies[25] from Europe and Japan have indicated that it is safe and well tolerated. We therefore undertook a controlled study to investigate its usefulness in preventing inappropriate vasoconstriction in patients with coronary artery disease. The following case history illustrates the results observed in one such patient in the protocol.

Case history: A 56 year old man with stable angina pectoris was referred to the Peter Bent Brigham Hospital for cardiac catheterization to determine the extent of his coronary artery disease. After giving informed consent, the patient underwent cardiac catheterization, which revealed severe three vessel coronary artery disease, with a 75 percent stenosis of the left anterior descending coronary artery, a 90 percent stenosis of the left circumflex artery, and total occlusion of the right coronary artery.

The patient underwent the cold pressor test after baseline arterial pressure, left ventricular end-diastolic pressure and coronary sinus flow were measured, and paired arterial and coronary sinus blood samples were obtained to determine myocardial extraction of oxygen and lactate. During the first 40 seconds of the test, the patient's arterial pressure increased from a mean of 108 to 126 mm Hg, and left ventricular end-diastolic pressure increased from 11 to 18 mm Hg. Despite the increase in arterial pressure, coronary blood flow decreased slightly from a baseline value of 102 to 97 ml/min at 40 seconds; coronary vascular resistance increased 30 percent. At this time, the patient experienced an attack of angina, and S-T segment depression appeared in the electrocardiographic tracing. The arterial-coronary sinus oxygen difference widened from 13.3 to 14.6 ml/100 ml, and net myocardial lactate production occurred.

After the patient's blood pressure and coronary sinus flow returned to baseline levels, we administered a 10 mg gelatin capsule of nifedipine, which the patient chewed for buccal absorption. Twenty minutes after administration of nifedipine, the cold pressor test was repeated.

Unlike the earlier results with the alpha adrenergic blocking drug phentolamine, the increase in blood pressure produced by the cold pressor stimulus was not prevented by nifedipine. The arterial pressure increased to approximately the same levels as it did during the control test, as did left ventricular end-diastolic pressure and myocardial oxygen consumption. However, coronary sinus blood flow increased from 108 to 130 ml/min, and coronary resistance decreased. Because ischemia was prevented, the patient experienced no chest pain, and the electrocardiogram, arterial-coronary sinus oxygen difference and lactate levels remained constant throughout the test.

Conclusions

Alpha adrenergic-mediated coronary vasoconstriction may play an important role in the pathogenesis of myocardial ischemia and angina pectoris. In patients with normal coronary arteries, the vasoconstrictor stimulus of the cold pressor test is compensated for by sensitive metabolic mechanisms that provide a substantial vasodilatory reserve. However, in patients with coronary artery disease, such mechanisms have already been partially utilized to maintain resting flow at a normal level. The imposition of a vasoconstrictor stimulus is thus relatively unopposed, and can result in a substantial decrease in coronary blood flow with the accompanying signs and symptoms of myocardial ischemia. The failure of conventional antianginal drugs to prevent this vasoconstriction is in keeping with their primary mode of action on the determinants of myocardial oxygen consumption, rather than on coronary resistance as such. The apparent specific effect of nifedipine on coronary vasospasm has led to the studies currently in progress, and preliminary results are promising, indicating that nifedipine can selectively block coronary vasoconstriction and thus may be a useful addition to the treatment of coronary artery disease.

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Nifedipine Therapy for Refractory Coronary Arterial Spasm

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Nifedipine was evaluated in the management of eight patients with intractable coronary arterial spasm. All had Prinzmetal's variant angina, normal or mildly abnormal coronary arteriograms, and a positive ergonovine maleate provocative test. Anginal attacks occurred at least three times a week in all patients during isosorbide dinitrate therapy. All patients had a decrease in frequency of ischemic attacks with nifedipine. Seven patients underwent repeat Holter monitor evaluation, which confirmed the absence of ischemic changes while they were taking nifedipine. When nifedipine dosage was decreased or therapy discontinued in six patients, all experienced a recurrence of anginal attacks. Two patients had minor side effects, which required a decrease in the dose of nifedipine. Nifedipine was well tolerated, and no major complications occurred with its use.

Nifedipine appears to be effective in the management of patients with symptomatic coronary arterial spasm and normal or mildly abnormal coronary arteriograms. Our data justify further investigation of nifedipine for treatment of such patients.

Patients with normal or mildly abnormal coronary arteriograms may suffer from Prinzmetal's variant angina due to coronary arterial spasm.[1–5] These patients often do not respond to isosorbide or propranolol therapy,[6,7] and coronary arterial bypass surgery is usually ineffective.[3,7,8] A few patients are refractory to all therapy and remain incapacitated.

Several investigators have suggested that nifedipine, an experimental drug, is effective in treatment of patients with Prinzmetal's variant angina and normal coronary arteriograms.[9–11] Therefore, we undertook a pilot study of nifedipine for the management of patients with intractable symptomatic coronary arterial spasm. The effects of therapy were evaluated by symptomatic response and electrocardiographic monitoring.

Methods

Patients: The study group (Table I) consisted of eight patients with Prinzmetal's variant angina due to spasm involving a normal or mildly abnormal coronary artery (less than 50 percent fixed narrowing of luminal diameter). Patients were included in this study only if they were unresponsive to isosorbide therapy (Table II). These patients were identified among approximately 27,000 patients who underwent coronary arteriography for suspected arteriosclerotic heart disease at the Cleveland Clinic between December 1972 and January 1979. During this period, a total of 21 patients were identified who had Prinzmetal's variant angina and normal or mildly abnormal coronary arteriograms, and 14 of these patients were unresponsive to vasodilator therapy. The eight patients who participated in this pilot study included six women and two men whose ages

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TABLE I

Clinical and Catheterization Findings

Case no.	Age (yr)* & Sex	Symptoms	Electrocardiogram: Resting	Electrocardiogram: During Spontaneous Ischemia	Catheterization: Coronary Arteries After NTG	Catheterization: Ergonovine Test
1	43, M	DRA, SA	Normal	S-T↑ II, III, aVF; 2:1 A-V block; VT	20% LCx; 10% RCA	100% RCA; S-T↑ II, III, aVF; angina
2	37, F	DRA, SA	Normal	S-T↑ II, III, aVF; sinus arrest; CHB	20% RCA; 10% LAD	S-T↑ II, III, aVF; angina; no repeat catheterization
3	36, F	NA, EA, CI	Normal	S-T↑ II, III, aVF	10% RCA	100% RCA; S-T↑ II, III, aVF; angina
4	52, F	DRA, NA, EA, CI	Normal	S-T↑ II, III, aVF; VT; 2:1 A-V block	40% RCA	100% RCA; S-T↑ II, III, aVF; 2:1 A-V block
5	37, F	DRA, NA, EA	Normal	S-T↑ II, III, aVF; VT	Normal	90% RCA; S-T↑ II, III, aVF; angina
6	39, F	DRA, NA, EA, CI, SA	Normal	S-T↑ V_1–V_5 or T wave changes V_1–V_5	20% LAD	100% AD; 50% RCA; S-T↑ V leads; angina
7	54, F	DRA, NA, SA	Normal	S-T↑ II, III, aVF; sinus arrest	Normal	100% RCA; 95% LAD, LCx; S-T↑ II, III, aVF; sinus arrest; angina
8	65, M	DRA, SA	Normal	S-T↑ II, III, aVF; VT; VF	40% RCA; 40% LCx	95% RCA; S-T↑ II, III, aVF

* Age at onset of symptoms.

A-V = atrioventricular; CHB = complete heart block; CI = coronary insufficiency; DRA = daytime resting angina; EA = exertional angina; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; NA = nocturnal angina; NTG = nitroglycerin; RCA = right coronary artery; SA = syncope with angina; VF = ventricular fibrillation; VT = ventricular tachycardia.

ranged from 35 to 65 years, with an average age of 45 years.

Prinzmetal's variant angina was defined as: (1) recurrent episodes of angina at rest; (2) transient S-T segment elevation during anginal attacks; and (3) normalization of the electrocardiogram between attacks, with no evidence of acute myocardial infarction.[12]

Diagnostic and therapeutic procedures: Coronary arteriography was performed with the Sones technique.[13] The ergonovine maleate provocative test for coronary arterial spasm was performed in all patients as previously described.[4] All patients were treated with isosorbide dinitrate, with a minimal dose of 30 mg sublingually or 40 mg orally a day. Seven patients received propranolol in doses of 80 to 160 mg/day. Five patients were treated with nitroglycerin ointment. Nifedipine was given initially in a dose of 10 mg orally four times a day. In two patients the dose was increased to 20 mg four times a day because of persistent angina. Informed consent was obtained from each patient before nifedipine was administered.

Data analysis: Patients were evaluated for frequency of angina every 1 to 3 months after treatment was started. Seven patients underwent long-term ambulatory electrocardiographic monitoring while taking nifedipine. The response to therapy was considered poor if the patient did not have a sustained decrease in frequency of anginal attacks for at least 1 month. The response was considered fair if less than a 50 percent reduction in the frequency of anginal attacks occurred and was considered good if anginal attacks were reduced in frequency by more than 50 percent.

Results

The results of the study are summarized in Tables I and II.

Ergonovine test: This provocative test reproduced the attacks of myocardial ischemia with S-T segment elevation in all patients. During the ergonovine test, seven patients underwent repeat coronary arteriography. This demonstrated coronary spasm with 90 to 100 percent obstruction in the artery supplying the area exhibiting S-T segment elevation. In one patient, the ergonovine test was performed the day after coronary arteriography, and angina and S-T segment elevation developed. Coronary arteriography revealed either

TABLE II

Medical Treatment of Coronary Arterial Spasm

Case no.	Isosorbide Dinitrate: Dose/Day (mg)	Isosorbide Dinitrate: Effect	Nitroglycerin Ointment: Dose/Day (inch)	Nitroglycerin Ointment: Effect	Propranolol: Dose/Day (mg)	Propranolol: Effect	Nifedipine: Dose/Day (mg)	Nifedipine: Additional Drugs	Nifedipine: Effect	Attacks/Month: Before Treatment	Attacks/Month: During Treatment
1	30, sl	Poor	None	. . .	160	Poor	80	None	Good	120	8
2	30, sl	Poor	8	Poor	80	Poor	40	Iso	Good	60	1
3	40, po	Poor	None	. . .	160	Fair	40	None	Good	12	2
4	30, sl	Poor	3	Poor	80	Poor	40	None	Good	80	1
5	125, po	Poor	1	Poor	80	Poor	40	None	Good	120	5
6	30, sl	Fair	6	Poor	80	Poor	80	Iso	Good	120	30
7	30, sl	Poor	None	. . .	160	Poor	40	None	Good	200	12
8	40, sl	Poor	6	Poor	None	. . .	40	None	Good	120	1

Iso = isosorbide dinitrate; po = orally; sl = sublingually.

normal coronary arteries or only mild obstructions in all patients.

Response to other drug therapy: None of the eight patients had a good response to isosorbide dinitrate or propranolol. A variety of other medications, including hydralazine, propantheline bromide, phenoxybenzamine, nylidrin, dipyridamole and clonidine, were tried unsuccessfully in these patients. In one patient, sublingual Hydergine® produced a good response.

Response to nifedipine: The response was considered good in all eight patients. The average number of anginal attacks decreased from 104 a month before nifedipine therapy to 8 a month during therapy. Two patients continued to have anginal attacks 8 to 30 times a month while taking nifedipine, 40 mg/day. Larger doses produced severe nausea in one patient, and the second patient had no further symptomatic improvement on 80 mg/day. One patient had a burning sensation in the hands and feet while taking 40 mg/day; these symptoms subsided when the dose was decreased to 30 mg/day. No symptoms of postural hypotension developed, and no serious side effects occurred in any patient. The duration of nifedipine therapy ranged from 2 to 38 months, averaging 21 months. Nifedipine was discontinued in two patients whose anginal attacks had subsided while they were taking the drug. However, a rapid increase in symptoms developed, and both patients required hospitalization. The symptoms in these patients were again controlled by the patients' resuming nifedipine therapy. The nifedipine dose was decreased in four patients, and all experienced an increased frequency of angina.

Illustrative Case Report

Case 4: A 53 year old woman was evaluated in February 1977 for a 6 month history of substernal tightness both at rest and on exertion. Her symptoms were relieved in 2 minutes by nitroglycerin. She had undergone lobectomy for squamous cell carcinoma of the lung in 1975. An electrocardiogram was normal. An X-ray film of the chest showed an elevated right hemidiaphragm. Propranolol and isosorbide dinitrate were administered, but the patient's chest pain subsequently increased in frequency, usually causing her to awaken at night. An exercise stress test showed normal findings.

Cardiac catheterization in May 1977 demonstrated 40 percent narrowing in the right coronary artery (Fig. 1A) and a normal left coronary artery and left ventricle. The next day, an electrocardiogram during angina at rest demonstrated S-T segment elevation in leads II, III and aVF (Fig. 2). After nitroglycerin was taken, the patient's chest pain subsided, and the electrocardiogram returned to normal. Continuous electrocardiographic monitoring revealed S-T segment elevation, sinus bradycardia, second degree atrioventricular block, and ventricular tachycardia during anginal attacks, which occurred eight times in 24 hours (Fig. 3). An ergonovine test during repeat coronary arteriography produced total obstruction of the "dominant" right coronary artery (Fig. 1B) and precipitated an attack of variant angina. The coronary spasm, symptoms and electrocardiographic changes subsided promptly after nitroglycerin was given.

Anginal attacks temporarily decreased to one a day when sublingual isosorbide dinitrate and nitroglycerin ointment were used. During the next 2 months, the anginal attacks increased to three a day. Nylidrin, 36 mg/day, and clonidine, 0.4 mg/day, did not relieve the symptoms. While the patient was taking Hydergine, 6 mg/day, the anginal attacks decreased to three a week. This drug (a combination of dihydroergocornine, dihydroergocristine and dihydroergokryptine) was discontinued because of expense.

Nifedipine, 10 mg four times a day, was started in August 1977, and all other medications were gradually discontinued. The patient remained nearly free of angina for 15 months. In November 1978, she had recurrent angina one or two times a day, beginning 1 week after she began to take imipramine hydrochloride, 75 mg/day, for depression. After this drug was

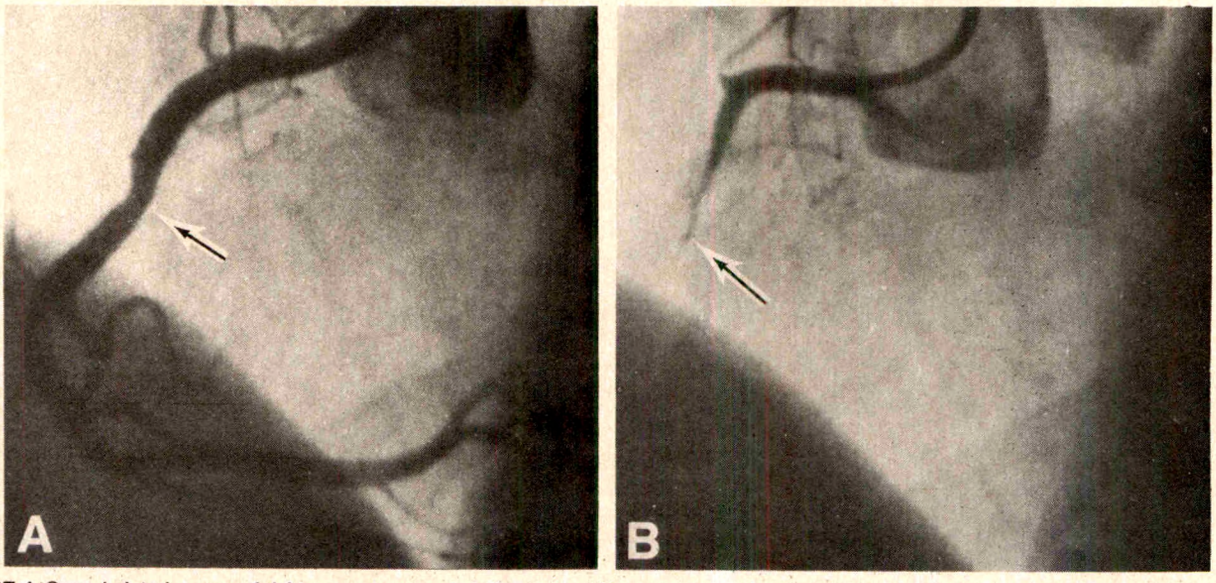

FIGURE 1. Case 4. Arteriograms of right coronary artery in left anterior oblique projection demonstrate localized 40 percent narrowing in the proximal right coronary artery (**arrow**) after nitroglycerin (**A**) and total obstruction in the same area (**arrow**) after ergonovine maleate (**B**). Angina and S-T segment elevation in the inferior electrocardiographic leads developed during spasm.

discontinued, the anginal attacks again subsided to less than one a month. A repeat 12 hour Holter monitor recording while the patient was receiving nifedipine revealed no episodes of S-T segment elevation or arrhythmia.

Discussion

This study was undertaken as a preliminary trial to evaluate nifedipine therapy for recurrent and intractable symptomatic coronary arterial spasm in patients with no fixed severe coronary obstructions. Our results suggest that nifedipine is safe, well tolerated, and effective in preventing ischemic attacks produced by coronary arterial spasm.

The study group: The study group comprised a homogeneous subset of patients with myocardial ischemia. All patients had Prinzmetal's variant angina, normal or mildly abnormal coronary arteriograms and a positive ergonovine maleate provocative test. This test, in patients with normal or nearly normal coronary arteriograms, has shown a high degree of specificity in detecting those who suffer from symptomatic coronary arterial spasm.[4,14–17] The ischemic attacks induced by the ergonovine maleate test in this study were similar to those that occurred spontaneously. Because all patients had normal or mildly abnormal coronary arteriograms, the symptoms in these patients cannot be attributed to a fixed severe coronary obstruction.

The patients in this study are not representative of typical patients with symptomatic coronary arterial spasm. Rather, they represent one extreme of the clinical spectrum, that is, patients with recurrent intractable angina.

Nitrate and beta adrenergic blocking drug therapy for coronary spasm: Long-acting nitrates are generally used for the treatment of patients with symptomatic coronary arterial spasm and no fixed severe coronary obstructions. Isolated case reports indicate that isosorbide dinitrate often appears effective in preventing attacks of Prinzmetal's variant angina in patients with normal coronary arteriograms.[1,5,18–21] However, in a larger number of case reports, such patients have not responded to isosorbide dinitrate.[1,9,22–27] Among reports describing five or more patients treated with isosorbide dinitrate, a good response to therapy occurred in less than 50 percent of patients.[6,7,28] The reports of therapy in patients with symptomatic coronary arterial spasm may be biased toward those with the more malignant and persistent forms of coronary spasm, because these are more obvious clinically and are more likely to be detected. This may account, in part, for the observation that isosorbide dinitrate does not appear

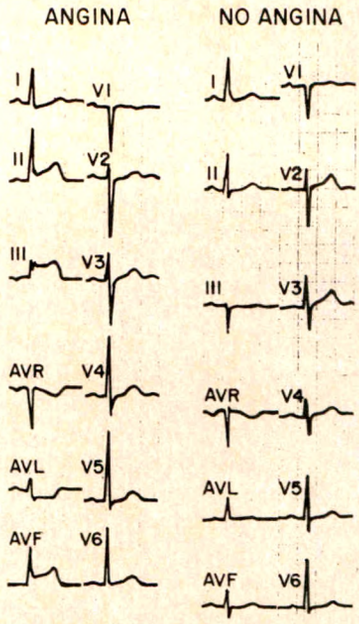

FIGURE 2. Case 4. Electrocardiograms demonstrating S-T segment elevation in inferior leads during Prinzmetal's variant angina (**left**) and return to normal after the angina subsided (**right**).

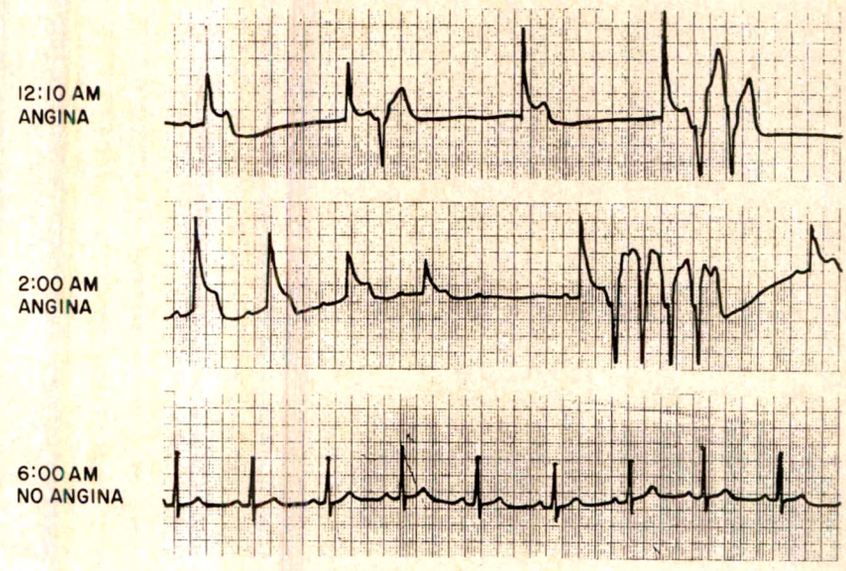

FIGURE 3. Case 4. Continuous electrocardiographic monitor recording of lead II. **Top,** during angina, S-T segment elevation, sinus arrest with junctional escape rhythm and premature ventricular complexes occurred. **Middle,** during another episode of angina, S-T segment elevation, Wenckebach phenomenon (atrioventricular block) and ventricular tachycardia occurred. **Bottom,** the electrocardiogram returned to normal when the patient was free of pain.

to be a satisfactory treatment for many patients with symptomatic coronary arterial spasm and normal coronary arteriograms. Among 21 patients with Prinzmetal's variant angina and normal or nearly normal coronary arteriograms evaluated at the Cleveland Clinic, only 7 (33 percent) had a good response to isosorbide dinitrate therapy. However, it is possible that more patients would have responded to isosorbide dinitrate if larger doses had been used.

Most patients with coronary arterial spasm do not respond to propranolol therapy,[1,3,9,22,24–27,29] although occasionally patients showed improvement, especially when propranolol was used in conjunction with isosorbide dinitrate.[18,30,31] In a few patients, propranolol therapy was associated with an increase in symptoms.[19,32,33] We believe that propranolol should be avoided or used with caution in patients with symptomatic coronary arterial spasm.

Other drugs for therapy of coronary spasm: Most patients with symptomatic coronary arterial spasm do not respond to phenoxybenzamine (Dibenzyline®)[1,25,26,31] or atropine,[1,9] although occasional successes have been reported with these drugs. Among the patients in this study, a variety of drugs, including hydralazine, propantheline bromide, nylidrin, clonidine, phenoxybenzamine and dipyridamole, were tried without success. Hydergine produced a marked decrease in symptoms in one patient (Case 4), but conclusions cannot be drawn from this one case.

Patients in whom ventricular tachycardia or fibrillation develops during coronary arterial spasm often fail to respond to lidocaine, quinidine sulfate or procainamide.[9,24,25] One patient in this study (Case 8) had recurrent ventricular tachycardia refractory to antiarrhythmic therapy. His attacks of ventricular tachycardia, which occurred only during episodes of S-T segment elevation, were controlled only when the episodes of coronary spasm and S-T segment elevation were prevented by administration of nifedipine.

One patient (Case 4) had a dramatic increase in angina coinciding with imipramine therapy. This finding suggests that imipramine, a tricyclic antidepressant, may provoke coronary arterial spasm. This effect could be due to the vasoconstrictor effect of tricyclic antidepressants, which block the uptake of norepinephrine at the cell membrane of adrenergic neurons,[34] or it may be produced by a drug interaction with nifedipine. Tricyclic antidepressants should be used with caution in patients who have symptomatic coronary arterial spasm.

Nifedipine and other calcium flux antagonists: Nifedipine is one of a group of calcium flux antagonists that also includes perhexiline maleate, verapamil and diltiazem. It is a dihydropyridine derivative that is structurally unrelated to existing antianginal drugs. It acts by blocking the transmembrane flux of calcium ions into the myocardial cell.[35] This, in turn, reduces the availability of intracellular free calcium ions, which are necessary for activation of the enzyme adenosine triphosphatase. Because the energy for muscle contraction is derived from the splitting of adenosine triphosphate by adenosine triphosphatase, nifedipine reduces contractility of the myocardial cell. It apparently acts in a similar manner on the smooth muscle of coronary arteries, causing coronary vasodilatation by inhibition of smooth muscle contraction. It produces preferential dilatation of coronary, cutaneous and muscular arteries.

Nifedipine is supplied in capsules containing 10 mg of the drug in solution. Approximately 90 percent of an orally administered dose is absorbed. It is excreted primarily by the kidneys, and its elimination half-life from serum is approximately 4 to 5 hours. The main side effects are headache (6 percent), vomiting (4 percent) and dizziness (3 percent).

Nifedipine has been widely used in Europe, South America and Asia for patients with typical angina as well as Prinzmetal's variant angina. Several investigators have evaluated nifedipine for treatment of patients with Prinzmetal's variant angina and normal coronary arteriograms. Hosoda and Kimura[11] found nifedipine effective in 12 of 17 patients; Goldberg et al.[10] reported good relief in three patients, partial relief in one and no effect in two; and Endo et al.[9] reported good results with nifedipine in 25 patients with Prinzmetal's variant angina, including 19 with no fixed severe obstructions.

Three other calcium flux antagonists have been investigated for therapy of symptomatic coronary arterial spasm. Verapamil,[26,36] perhexiline maleate,[32,37] and diltiazem[38] have been reported to be effective in the treatment of patients with Prinzmetal's variant angina and no fixed severe obstructions.

Implications: Our experience with nifedipine in eight patients with symptomatic coronary spasm who were unresponsive to other medications is encouraging. This drug was highly effective in controlling symptoms and preventing S-T segment elevation in all patients. However, three patients continued to have attacks of angina from 8 to 30 times a month. No major side effects occurred as a result of nifedipine therapy, although one patient experienced nausea when the dose was increased to 80 mg/day, and another complained of a burning sensation in the hands and feet on a dosage of 40 mg/day. The data accumulated in this pilot study justify further trials of nifedipine for the management of patients with symptomatic coronary arterial spasm.

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Nifedipine in the Treatment of Prinzmetal's (Variant) Angina

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The clinical response to therapy with the calcium-blocking agent nifedipine was assessed in 12 patients with variant angina pectoris who were 44 to 67 years old. Five patients had vasospasm of the left anterior descending coronary artery, and seven had spasm of a dominant right coronary artery. Before nifedipine therapy, the frequency of anginal attacks per 24 hour period ranged from 1 to 12, with ventricular tachycardia accompanying ischemic episodes in 7 of 12 patients and high grade atrioventricular block occurring in 2 patients. After therapy with nifedipine, 11 of 12 patients had initial relief of symptoms, and 7 of the 11 had long-term relief. Withdrawal of nifedipine led to recurrence of angina on six occasions in four patients. Provocative testing in the cardiac catheterization laboratory by means of the cold pressor test in one patient and ergonovine maleate in another before and after nifedipine administration showed that this agent can block both alpha adrenergic- and ergonovine-induced vasospasm. Nifedipine may have a significant role in the therapy of angina caused by coronary spasm.

Myocardial ischemia in man is now known to be caused by either or both of the following mechanisms: (1) a primary increase in myocardial oxygen demand that is not accompanied by an adequate increase in myocardial oxygen supply, as occurs in fixed obstructive coronary artery disease with exertional or pacing-induced angina[1]; or (2) a primary reduction in myocardial oxygen supply due to an abrupt reduction in coronary blood flow, as occurs in coronary arterial spasm.[2–5] Because coronary spasm may be caused by a variety of stimuli that have as their final common pathway the calcium-mediated contraction of coronary arterial smooth muscle, we studied the effects of the calcium-blocking agent nifedipine in 12 patients with variant angina. The clinical response of these 12 patients, along with the effect of nifedipine on cold-pressor- and ergonovine-induced coronary vasospasm, forms the basis of this report.

Methods

Patient selection: The criteria for inclusion of the patients in this study were: (1) a history of angina at rest associated with S-T segment alterations in the electrocardiogram; (2) coronary arterial spasm with or without fixed obstructive lesions demonstrated with selective coronary arteriography; (3) prior failure of conventional therapy with long- and short-acting nitrates; and (4) informed consent for the administration of nifedipine.

Catheterization: Cardiac catheterization and selective coronary arteriography were performed with the Judkins technique. Provocative testing for coronary spasm with ergonovine maleate was carried out in 8 patients as follows: Ergonovine maleate was given as a 0.05 mg bolus dose intravenously every 2 minutes until electrocardiographic changes and typical angina occurred; then a second angiogram of the coronary artery clinically thought to be affected by spasm was obtained. Nitroglycerin was then given sublingually or intravenously, or both,

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until the electrocardiographic changes and the angina resolved. A third cineangiogram followed nitroglycerin administration. In one patient the cold pressor test was used to provoke spasm, and in three patients another spasm occurred spontaneously.

Nifedipine administration: Forty to 120 mg of nifedipine was administered in divided doses every 4 to 6 hours (120 mg/day is the maximal dose recommended by the manufacturer). In each patient the dosage was gradually increased until relief of symptoms occurred or the maximal dose had been administered. Nitrate therapy was initially continued during nifedipine administration. Nitrates were administered in the maximal dose tolerated by the patient and consisted of a combination of isosorbide dinitrate and nitropaste in addition to sublingual nitroglycerin.

In one patient (Patient 10) the efficacy of nifedipine therapy was further tested in the catheterization laboratory by a second application of the cold pressor test while the patient was receiving nifedipine. Another patient (Patient 12), who had ergonovine-induced vasospasm, was rechallenged with this agent after the acute administration of nifedipine.

Clinical characteristics of patient population (Table I): Five women and seven men aged 44 to 67 years met the criteria for inclusion in the study. Angina at rest was present in all patients, and an exertional component was present in two. The duration of angina at rest ranged from1 week to 72 months. Ventricular tachycardia occurred during ischemic episodes in 7 of 12 patients. High grade atrioventricular (A-V) block during ischemia occurred in two patients, both of whom had right coronary artery spasm. Spasm of the left anterior descending coronary artery occurred in five patients, and spasm of the right coronary artery recurred in the remaining seven patients. Fixed obstructive lesions of hemodynamic significance (narrowing of luminal diameter by at least 50 percent) were present in the coronary artery affected by spasm in 2 of 12 patients. Coronary spasm was provoked in 8 of 12 patients by means of ergonovine maleate in total doses ranging from 0.10 to 0.20 mg. Left ventricular function was normal in all patients except Patient 9. This patient, who had had an anterior myocardial infarction 3 weeks before the study, had an anterior ventricular aneurysm and reduced ejection fraction of 44 percent.

TABLE I

Clinical Characteristics of 12 Patients

Case no.	Age (yr) & Sex	Anginal Pattern	Electrocardiographic Features	Catheterization Data	Initial Response to Nifedipine
1	46F	Resting angina × 7 days; 4 attacks/day prior to cath	S-T ↑ II, III, aVF; VT	Normal LVF; normal CA's; RCA spasm (E)	Pain-free, 60 mg/day
2	67F	Exertional angina × 7.5 yr; resting angina × 3 yr; 2 attacks/day prior to cath	S-T ↑ II, III, aVF; VT	Normal LVF; 60% RCA lesion; RCA spasm (S)	Pain-free, 60 mg/day
3	43M	Resting angina × 2 mo; 4 attacks/day prior to cath	S-T ↑ V_1–V_6; VT	Normal LVF; normal CA's; LAD spasm (S)	Pain-free, 120 mg/day
4	62M	Resting angina × 19 mo; 12 attacks/day prior to cath	S-T ↑ V_1–V_6; S-T ↓ V_1–V_6; VT	Normal LVF; 50% LAD lesion; 60% RCA lesion; LAD spasm (E)	Pain-free, 140 mg/day
5	52M	2 yr of exertional and resting angina; 3 attacks/day prior to cath	S-T ↑ II, III, aVF; VT	Normal LVF; 50% LAD lesion; RCA spasm (E)	Pain-free, 60 mg/day
6	46F	Resting angina × 6 mo; 1 attack/day prior to cath	S-T ↑ V_1–V_6; VT	Normal LVF; 30% LAD lesion; 30% RCA lesion; LAD spasm (E)	Pain-free, 60 mg/day
7	58M	Resting angina × 1 mo; 3 attacks/day prior to cath	S-T ↑ V_1–V_6	Normal LVF; normal CAs; LAD spasm (E)	No effect
8	52M	Resting and exertional angina × 6 yr; 6 attacks/day prior to cath	S-T ↑ V_1–V_6	Normal LVF; normal CAs; LAD spasm (S)	Pain-free, 80 mg/day
9	46M	Resting angina × 2 mo; 3 attacks/day prior to cath	Anterior scar; S-T ↑ II, III, aVF; S-T ↓ II, III, aVF; VT; A-V block	Anterior aneurysm; total occlusion; LAD; 50% LCx; normal dominant RCA; RCA spasm (E)	Pain-free, 120 mg/day
10	53F	Resting angina × 3.5 yr; 3 attacks/day prior to cath	S-T ↑ II, III, aVF; S-T ↓ II, III, aVF; A-V block	Normal LVF; 70% LAD lesion; RCA spasm (CP)	Pain-free, 120 mg/day
11	44F	Resting angina × 1 mo; 2 attacks/day prior to cath	S-T ↑ II, III, aVF	Normal LVF; normal CAs; RCA spasm (E)	Pain-free, 40 mg/day
12	56M	Resting angina × 8 mo; 1 attack/day prior to cath	S-T ↑ II, III, aVF	Normal LVF; normal CAs; RCA spasm (E)	Pain-free, 40 mg/day

A-V = atrioventricular; CAs = coronary arteries; cath = cardiac catheterization; (CP) = cold pressor-induced spasm; (E) = ergonovine-induced spasm; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LVF = left ventricular function; RCA = right coronary artery; (S) = spontaneous spasm; S-T ↑ and S-T ↓ = S-T segment elevation and depression, respectively.

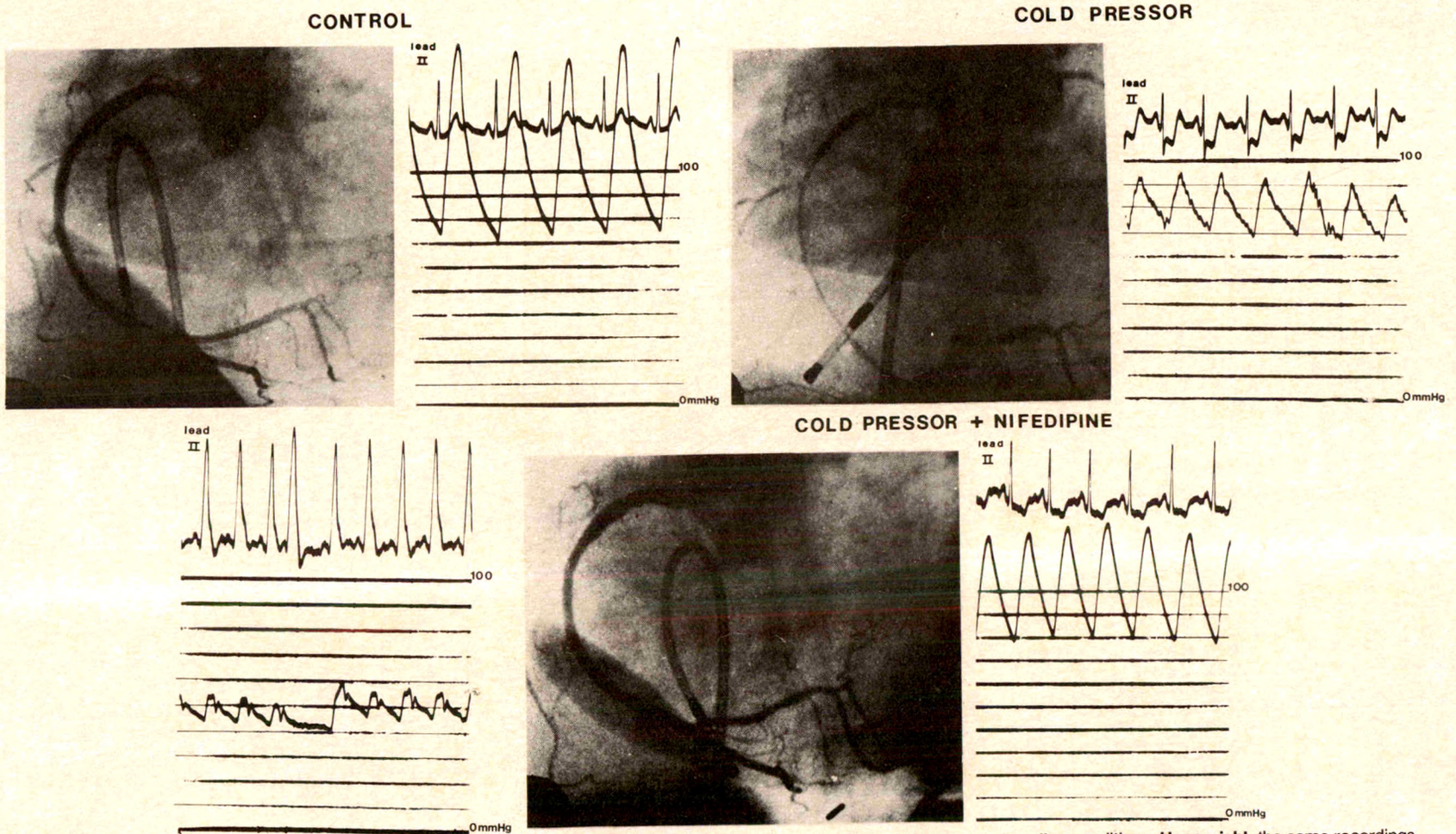

FIGURE 1. Patient 10. **Upper left,** lead II electrocardiogram, aortic pressure tracing and right coronary angiogram taken under baseline conditions. **Upper right,** the same recordings after the cold pressor test. Lead II shows S-T segment depression; there is a decrease in aortic pressure from the control level; and the right coronary angiogram shows severe spasm. **Lower left,** 1 minute later. Lead II now shows S-T segment elevation, and there is severe hypotension. These changes reverted to baseline levels after nitroglycerin administration. **Lower right,** after nifedipine administration a repeat cold pressor test was carried out. Lead II shows only mild S-T segment depression; the aortic pressure is stable; and the right coronary arterial angiogram is unchanged from the control study.

Results

Initial clinical response to nifedipine administration (Table I): Before nifedipine therapy, the frequency of anginal episodes for the entire group of 12 patients ranged from 1 to 12/day. Within 24 to 48 hours of selection of the optimal nifedipine dose, pain at rest disappeared in 11 of 12 subjects. Clinically adverse hypotension or tachycardia was not observed, and no acute side effects were observed. After the administration of the optimal nifedipine dose, concomitant nitrate therapy was withdrawn in four patients.

Provocative invasive testing before and after nifedipine: In Patient 10 the efficacy of nifedipine was further evaluated with the cold pressor test in the catheterization laboratory. With the patient asymptomatic at the beginning of the test, results of hemodynamic and angiographic studies were normal (Fig. 1, upper left). After immersion of the patient's hand in ice water for 63 seconds (Fig. 1, upper right), marked S-T segment depression in lead II, hypotension and crushing retrosternal pain developed; a repeat right coronary angiogram taken a few seconds later showed severe spasm. Approximately 1 minute later (Fig. 1, lower left) S-T segment elevation had replaced depression in lead II, and aortic pressure had decreased to 50/40 mm Hg. Relief was obtained after sublingual administration of five 0.3 mg nitroglycerin tablets. The patient, who was having three episodes of angina per day, was then given 120 mg of nifedipine per day in addition to nitrates, and was rechallenged with the cold pressor test (Fig. 1, lower right). At this time angina did not develop, the lead II electrocardiogram showed only minor S-T segment depression, the aortic pressure was normal, and no spasm was seen in the right coronary artery.

In Patient 12, the ability of nifedipine to block ergonovine-induced vasospasm was demonstrated: Two cardiac catheterization procedures were performed. The

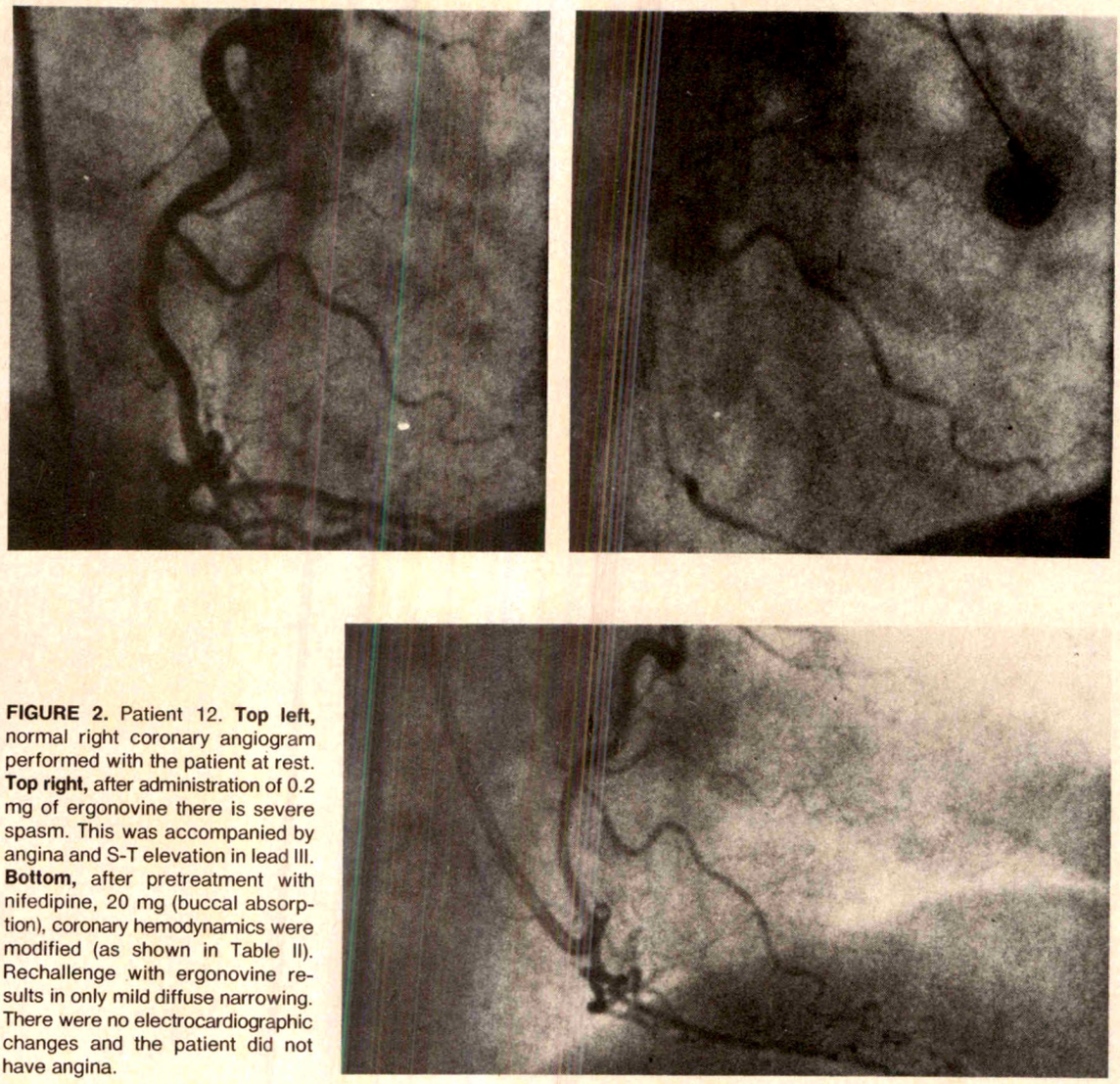

FIGURE 2. Patient 12. **Top left,** normal right coronary angiogram performed with the patient at rest. **Top right,** after administration of 0.2 mg of ergonovine there is severe spasm. This was accompanied by angina and S-T elevation in lead III. **Bottom,** after pretreatment with nifedipine, 20 mg (buccal absorption), coronary hemodynamics were modified (as shown in Table II). Rechallenge with ergonovine results in only mild diffuse narrowing. There were no electrocardiographic changes and the patient did not have angina.

baseline right coronary angiogram with the patient asymptomatic and at rest was normal (Fig. 2, top left). After the administration of a total of 0.2 mg of ergonovine (four 0.05 mg bolus injections), the patient's typical angina developed along with S-T segment elevation seen in leads II, III and aVF and a decrease in blood pressure from 150/80 to 90/60 mm Hg. At this time the coronary angiogram showed severe right coronary arterial spasm (Fig. 2, top right). These changes were reversed by sublingual administration of nitroglycerin. At the second catheterization procedure coronary hemodynamic values were measured before and after administration of 20 mg of nifedipine (buccal absorption) (Table II). Resting mean arterial pressure was 120 mm Hg and coronary blood flow (measured with the thermodilution technique) was 117 ml/min. Twenty minutes after nifedipine administration, mean arterial pressure decreased to 100 mm Hg and coronary blood flow increased to 164 ml/min. Concomitantly, the myocardial arteriovenous oxygen difference narrowed from a control value of 63 to 50 percent. At this point, repeat challenge with ergonovine was carried out at the same 0.2 mg dose that had previously produced spasm. The patient remained asymptomatic, there were no electrocardiographic changes and the repeat coronary angiogram (Fig. 2, bottom) showed only mild, diffuse narrowing, that is, the normal angiographic response to ergonovine.[5]

Long-term follow-up study (Table III): The long-term follow-up results varied in the 11 patients who had shown an excellent initial response to nifedipine. Seven of these 11 patients continued to have an excellent response and were either asymptomatic or had only infrequent anginal episodes easily relieved by nitroglycerin. The follow-up period for the seven patients ranged from 2 to 17 months, and the dose of nifedipine ranged from 40 to 120 mg/day.

The effects of nifedipine therapy are dramatically demonstrated by Patient 4 (Fig. 3). Before the administration of nifedipine, this patient had 12 attacks daily for approximately 1 week, with ventricular tachycardia accompanying the ischemic episodes. Coronary arteriography revealed a fixed 50 percent stenosis of the proximal left anterior descending coronary artery. After ergonovine administration, transient total occlusion of this artery was produced, starting at the fixed lesion. The patient continued to have attacks despite therapy with long- and short-acting nitrates. After administration of 40 mg/day of nifedipine, the patient's anginal syndrome was completely abolished for a period of 4 months. However, headache and digital dysesthesias developed during therapy and the patient decided to discontinue nifedipine therapy. Within 3 days, severe episodes of the typical angina recurred at a frequency of 4/day and a total of 8 episodes in 48 hours. Nifedipine was administered, and the patient became asymptomatic for 2 months. He again chose to discontinue use of nifedipine because of side effects and became severely symptomatic, having four attacks of angina a day. He again resumed therapy with nifedipine and has now been symptom-free for 9 months. Concomitant administration of 80 mg/day of propranolol has decreased the severity of the headaches. Follow-up history, physical examination and chest X-ray films in this patient have shown no evidence of heart failure despite simultaneous administration of a calcium antagonist and a beta adrenergic blocking agent.

The remaining four patients included one patient (Patient 3) with normal coronary arteries who had an acute myocardial infarction after nitrate withdrawal during nifedipine therapy. The second patient (Patient 8) died suddenly after 1 month of nifedipine therapy. This patient had recurrence of variant angina and associated ventricular arrhythmias despite nifedipine therapy. Two attempts to discontinue nifedipine led to worsening of his symptoms. In a third patient (Patient

TABLE II

Patient 12. Coronary Hemodynamic Effects of Acute Nifedipine Administration Prior to Ergonovine Rechallenge

	Control	Nifedipine
MAP (mm Hg)	120	100
CBF (ml/min)	117	164
CVR (mm Hg/ml per min)	1.03	0.61
a-v O_2 Δ (%)	63	50

a-v O_2 Δ = myocardial arteriovenous oxygen difference; CBF = coronary blood flow; CVR = coronary vascular resistance; MAP = mean arterial pressure.

TABLE III

Long-Term Follow-Up Study of 12 Patients

Case no.	Nifedipine Dose (mg/day)	Follow-Up Period (mo)	Clinical Status
1	60	9	No angina
2	60	17	No angina
3	120	1	Myocardial infarction after nitrate withdrawal
4	40	15	No angina; headache, digital dysesthesias on drug
5	120	2	Occasional resting angina; 8 nitroglycerin/mo
6	120	13	Occasional resting angina; 5 nitroglycerin/mo
7	No response to initial nifedipine		
8	80	1	Died suddenly
9	120	3/4	Recurrence of attacks on nifedipine; required surgery on non-diseased coronary artery (ligation and bypass)
10	120	2	Angina-free on drug; leg cramps and headache required drug withdrawal; angina recurred
11	60	5	No angina; mild fatigue, headache, perspiration on drug
12	40	5	Pain-free

9), who had had a prior anterior myocardial infarction, right coronary arterial spasm developed. This patient had an initially encouraging response to nifedipine, but he had recurrence of one episode of angina a day accompanied by ventricular tachycardia while he was receiving the drug. An attempt to change to perhexiline therapy resulted in recurrence of more frequent and severe episodes when nifedipine was withdrawn. This patient was finally treated by ligation of the nondiseased right coronary artery proximally and saphenous vein bypass grafting into the distal right coronary artery, past the point of angiographically demonstrated focal spasm. Another patient (Patient 10) discontinued nifedipine therapy because of headache, leg cramps and flushing—symptoms possibly related to the peripheral vasodilatory effects of the drug. These symptoms antedated nifedipine therapy but became more severe during administration of the drug. This patient has had recurrence of resting angina after withdrawal of nifedipine, and subsequently died during coronary bypass surgery at another institution.

Discussion

The main findings of this study are (1) The addition of nifedipine to nitrates is efficacious in the initial therapy of refractory variant angina. (2) There were no major *initial* side effects due to nifedipine administration; specifically, clinically adverse hypotension or tachycardia was not observed and, in addition, none of the patients had symptoms of congestive heart failure, a possible side effect of therapy with calcium-blocking agents. (3) Nifedipine withdrawal is associated with recurrence of angina, an effect that was demonstrated on six occasions in four patients. (4) Nifedipine not only can suppress spontaneous symptoms, but it also can block cold pressor- and ergonovine-induced coronary vasospasm. The cold pressor test is an alpha adrenergic stimulus that has been shown to increase coronary vascular resistance[6,7] and to induce coronary vasospasm,[8] whereas ergonovine is a specific and sensitive agent for provocation of spasm in patients with variant angina.[5]

Previous investigations on treatment of coronary spasm: The renewed interest in coronary vasospasm as a possible etiologic factor in unstable angina[9,10] and acute myocardial infarction[11–13] had led investigators to use various agents in an attempt to block smooth muscle contraction of the epicardial coronary arteries. The rationale for the use of calcium antagonistic agents in the therapy of coronary spasm is based on their ability to impede movement of calcium ions during excitation-contraction coupling in vascular smooth muscle.[14,15] For example, coronary spasm was induced in a series of 10 patients by increasing pH via hyperventilation and Tris buffer infusion.[16] These maneuvers cause a decrease in local hydrogen ion concentration, which presumably leads to less competition with calcium ions and hence promotes coronary arterial smooth muscle spasm. Diltiazem, a calcium antagonist, was demonstrated to suppress coronary vasospasm in five patients who received the drug.[16] Encouraging clinical results were also reported in preliminary investigations utilizing the calcium-blocking agents verapamil,[17] perhexiline[18] and nifedipine.[19]

Therapeutic implications: The use of calcium-blocking agents in the therapy of coronary vasospasm offers a new therapeutic approach to this problem. Previous studies have suggested that a primary decrease in coronary blood flow and increase in coronary vascular resistance, accompanied by a widening of the myocardial arteriovenous oxygen difference, contribute to both cold-induced[6,7] and ergonovine-induced[5] angina. Nifedipine has the opposite effects: It increases coronary blood flow, reduces coronary vascular resistance and narrows the myocardial arteriovenous oxygen difference.[20] These effects were dramatically demonstrated in Patient 12 (Table II) before rechallenge with ergonovine.

The observation that S-T segment depression may precede S-T segment elevation early in the course of spasm lends further support to the concept that coronary vasospasm may cause unstable angina with S-T segment *depression* in patients with severe fixed coronary disease. Thus, it is possible that calcium-blocking vasodilators will prove useful in a variety of clinical settings, including variant angina with or without coexistent atherosclerotic disease, unstable angina with S-T segment depression, and acute myocardial infarction.

Although initial drug efficacy is dramatic, long-term results are less clear-cut. We have observed the long-

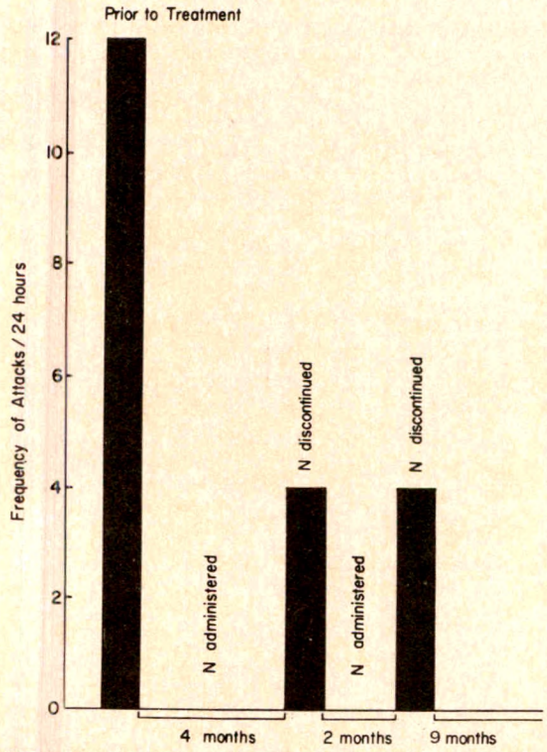

FIGURE 3. Clinical course of Patient 4. Each episode of nifedipine (N) withdrawal resulted in recurrence of ischemic symptoms. Reinstitution of nifedipine therapy promptly prevented anginal episodes.

term side effects of headache, digital dysesthesias, leg cramps and flushing. These effects may be caused by the systemic vasodilatory effect of the drug. In addition, because nifedipine interferes with excitation-contraction coupling in cardiac as well as smooth muscle, the potential for a deleterious effect on myocardial performance needs to be assessed. Although we did not observe symptoms of heart failure, either in a patient with a recent anterior infarction or in a patient simultaneously receiving a beta adrenergic blocking agent, the hemodynamic effects of this new agent need to be studied in a variety of patients. No attempt was made in the present study to compare prospectively the efficacy of long-term acting nitrates with that of nifedipine. Rather, nitrate therapy was initially continued simultaneously with nifedipine administration. Gradual reduction of nitrates was associated with a myocardial infarction in one patient (Patient 3), but had no ill effects in three other patients in whom the drug was withdrawn (Patients 4, 11 and 12). In addition, because the frequency of anginal attacks varies and the frequency of coronary spasm may spontaneously resolve, further prospective studies utilizing clinical response and provocative testing in the catheterization laboratory will be needed to assess the true efficacy of nifedipine in patients with variant angina and in other clinical settings where coronary vasospasm may be an important etiologic factor.

Acknowledgment

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Nifedipine Therapy for Stable Angina Pectoris: Preliminary Results of Effects on Angina Frequency and Treadmill Exercise Response

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Ten patients with stable angina pectoris secondary to atherosclerotic coronary artery disease received nifedipine (10 mg and 20 mg orally three times daily, each for 2 weeks) or placebo (for 2 weeks) in a single-blind manner during a 6 week period. One patient was excluded because nocturnal and resting angina developed while he was receiving placebo. The frequency of anginal attacks in the remaining nine patients decreased from 11.2 ± 2.2 (mean ± standard error of the mean) per patient per week during administration of placebo to 7.1 ± 1.6 during therapy with nifedipine at 10 mg and to 6.3 ± 1.7 during administration of 20 mg of nifedipine ($P < 0.05$ for both doses of active drug versus placebo). Nitroglycerin consumption similarly decreased from 8.9 ± 2.3 tablets per patient per week (placebo) to 4.8 ± 1.4 tablets during administration of 10 mg of nifedipine and to 4.2 ± 1.2 during therapy with 20 mg of the drug ($P < 0.05$ for both doses of drug versus placebo). Duration of treadmill exercise increased from 368 ± 50 seconds (placebo) to 471 ± 72 seconds at the 10 mg dose of nifedipine and 522 ± 79 seconds at 20 mg ($P < 0.05$ for both doses versus placebo). Maximal S-T segment shift and product of heart rate × systolic blood pressure did not differ between the placebo period and that of active drug therapy. Treadmill exercise performed during subsequent double-blind, randomized crossover treatment with placebo and nifedipine revealed increased exercise duration after nifedipine therapy (524 ± 49 seconds) compared with that after placebo (462 ± 52 seconds) ($P < 0.005$) but, again, maximal S-T shift and the product of heart rate × systolic blood pressure did not differ. Side effects from nifedipine were minor and easily tolerable. The results seem to indicate that nifedipine prolongs exercise time by decreasing heart rate × systolic blood pressure product at a given work load, possibly in a manner similar to that of long-acting nitrate therapy.

Current drug therapy for the prevention of angina pectoris in patients with coronary atherosclerosis relies on the use of nitrates and beta adrenergic blocking agents. These medications reduce the determinants of myocardial oxygen consumption at a given level of activity and prolong the total time to onset of angina.[1–5] Beta receptor blockade lessens heart rate and potentially decreases inotropy, while nitrates decrease left ventricular wall tension. There is evidence that nitroglycerin causes coronary vasodilation,[6,7] but this mechanism has not yet been proved conclusively to be of major benefit.[8,9] Recently, a new class of antianginal drugs that inhibit the inward passage of calcium across myocardial and vascular smooth muscle cell membranes has been introduced. Because the passage of calcium to the inside of cells is necessary for excitation-

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contraction coupling, these drugs (calcium antagonists) have been found to cause coronary arterial smooth muscle relaxation and to decrease coronary vascular resistance in animals.[10,11] Another effect of these agents is a decrease in peripheral arteriolar resistance, which results in lowering of blood pressure.[12] At higher dosages, myocardial contractility and oxygen consumption may decrease.[13] These actions may conceivably be helpful in the treatment of angina pectoris. An additional possible effect of the calcium antagonists is the alteration of action potentials within the heart's specialized conduction system.[13]

Among the calcium antagonists, nifedipine, a 1, 4-dihydropyridine derivative, has been extensively evaluated in the laboratory and tested in many patients. Experience with nifedipine outside of the United States[14,15] in patients with coronary artery disease indicates that it is useful in decreasing the incidence of anginal episodes and increasing treadmill exercise time. This report covers the initial outcome of nifedipine therapy compared with placebo during the first 6 weeks of a 20 week study of patients with coronary artery disease and stable angina pectoris, and gives results of exercise testing performed during weeks 7 through 20.

Methods

Patients: Ten men ranging in age from 44 to 74 years (mean 57 years) were studied. The study was approved by the Clinical Investigation Committee of the Milton S. Hershey Medical Center, and written informed consent was obtained from the patients. All subjects gave a history of classic angina pectoris occurring in a stable pattern for 3 months, and no patient had had a myocardial infarct within the previous 6 months. Patients with hypertension, congestive heart failure or clinically significant medical illness other than atherosclerotic coronary disease and those receiving digitalis, diuretic or antiarrhythmic agents, tranquilizers, antidepressants or central nervous system stimulants were excluded. Administration of long-acting nitrates and beta adrenergic blocking drugs was gradually reduced and discontinued 24 to 48 hours before initiation of the protocol. In addition to taking nifedipine or placebo, the subjects took nitroglycerin sublingually as needed for relief of angina.

All patients had a documented history of previous transmural myocardial infarction or a coronary arteriogram showing 70 percent or greater narrowing of at least one major coronary artery. Four subjects had prior infarction alone (anterior in one, anterior-inferior in two, and inferior in one). Four patients had coronary stenosis verified with coronary arteriography; of these, three had single vessel disease and one had double vessel disease. Two persons had undergone coronary arterial bypass surgery for triple vessel disease and had recurrent angina. Graft patency was previously assessed in one of these patients with arteriography, which had revealed obstruction of one of two bypass grafts.

Exercise testing: Electrocardiographic leads II, III and V_5 were analyzed during exercise, and the same lead that demonstrated S-T shift (eight patients) or J point shift (one patient) during the first 2 weeks was used for repeat measurements during subsequent tests. Patients with left bundle branch block or repolarization abnormalities altering the S-T segment were excluded. Each patient demonstrated 1 mm horizontal or downward sloping S-T segment depression 0.08 second after the J point, 2 mm J point depression with an upward sloping S-T segment, or 1 mm S-T segment elevation during treadmill exercise testing on two occasions during the first 2 weeks of study. Exercise was performed approximately 3 hours after the patient received nifedipine or placebo. The protocol for treadmill exercise testing consisted of 3 minute stages beginning at 2.0 miles/hour, 3 percent grade, and increasing after completion to 3.3 miles/hour, 6 percent grade. Thereafter, speed remained fixed at 3.3 miles/hour, while the grade increased by 3 percent increments at each stage. Blood pressure was measured by cuff at each minute of exercise.* Exercise was discontinued when angina of moderate severity occurred or when the patient could no longer continue because of dyspnea or fatigue.

Drug protocol: The data presented in this report are the preliminary results obtained during a 20 week protocol, during which placebo or nifedipine was dispensed. During the first 2 weeks, placebo was given (1 capsule every 8 hours). During weeks 3 and 4, nifedipine, 10 mg orally every 8 hours, was administered; subsequently, nifedipine, 20 mg orally every 8 hours, was given during weeks 5 and 6. Thereafter, a 1 week "washout" (placebo) period ensued, followed by two 6 week treatment periods of nifedipine or placebo administered in a random, double-blind manner. The double-blind treatment periods were separated by a week of placebo. Exercise tests were performed at the end of weeks 1, 2, 4 and 6 as well as during weeks 9, 13, 16 and 20 of the double-blind treatment periods. Each subject recorded in a diary all episodes of angina and the number of nitroglycerin tablets consumed.

Statistical analysis: The Friedman analysis of variance for ranked data was used to assess the effects of placebo and nifedipine at each of the two dose levels.[16] The Wilcoxon-Wilcox test was used as a multiple range test for the comparison of individual pairs of groups.[16] The Wilcoxon signed rank test was used to compare paired data not previously subjected to the Friedman test.[16] P values of ≤ 0.05 were considered significant.

Results

Side effects: Nocturnal and resting angina developed in one patient at the end of the 2nd week of placebo; the data from this subject were excluded from analysis. Of the nine remaining patients who completed the 6 week protocol, fatigue developed in four, two experienced dizziness, one had tinnitus and one had nasal congestion. These symptoms were easily tolerated and reduction in dosage was not required. No adverse electrocardiographic effects were noted.

Frequency of angina and nitroglycerin consumption (Fig. 1): The mean frequency of anginal episodes was 11.2 ± 2.2 (mean ± standard error of the mean) per patient per week during 2 weeks of placebo, 7.1 ± 1.6 during the period of administration of 10 mg of nifedipine, and 6.3 ± 1.7 while 20 mg of active drug was given. Each patient studied responded to nifedipine with a decrease in recorded anginal attacks at the 10 mg dose. A nonrandom grouping of data was seen by the analysis of variance ($P < 0.005$). Nifedipine, in doses of 10 mg and 20 mg, caused a significant decrease in an-

* The mean standard deviation of repeated blood pressure measurements (18 different measurements on nine subjects obtained on two different occasions) was 6 mm Hg at rest and 16 mm Hg during the 4th minute of exercise.

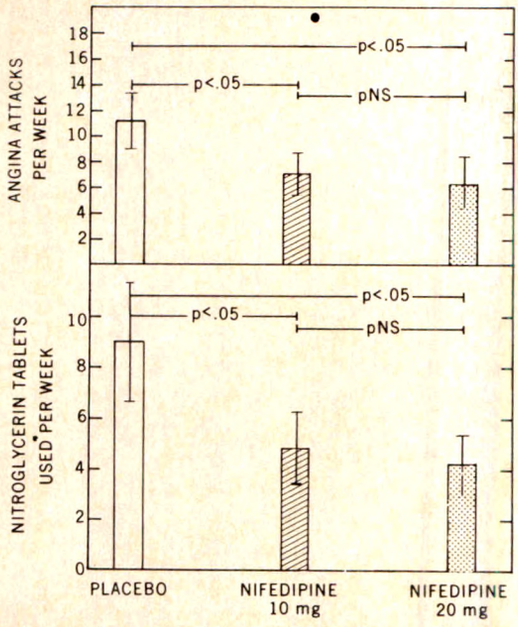

FIGURE 1. Effect of nifedipine therapy (10 mg and 20 mg orally every 8 hours) compared with that of placebo on frequency of anginal attacks and nitroglycerin used per week. Values are mean ± standard error of the mean. NS = not significant; p = probability.

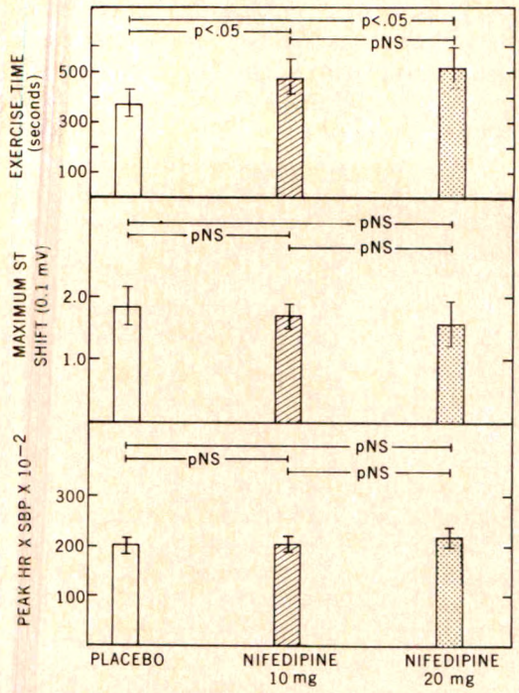

FIGURE 2. Effect of nifedipine therapy (10 mg and 20 mg orally every 8 hours) on peak treadmill exercise time, maximal S-T segment shift and product of heart rate and systolic blood pressure (HR × SBP) at peak exercise. Unidentified abbreviations as in Figure 1.

ginal frequency when compared with that in patients on placebo (both $P < 0.05$ vs. placebo), but for each dose the decrease was essentially the same (P value not significant).

Nitroglycerin consumption averaged 8.9 ± 2.3 tablets per patient per week for the 2 weeks of placebo administration, 4.8 ± 1.4 during the period in which 10 mg of nifedipine was taken, and 4.2 ± 1.2 during therapy with 20 mg of nifedipine. As with anginal frequency, there was decreased nitroglycerin consumption in each subject receiving 10 mg of nifedipine. A significant difference existed among the three groups ($P < 0.005$). Both 10 mg and 20 mg of nifedipine caused a decrease in nitroglycerin consumption, when compared with that taken during administration of placebo (both $P < 0.05$). However, there was no difference in nitroglycerin usage between the two different doses of the drug (P value not significant).

Treadmill exercise response (Fig. 2): Mean exercise time was 361 ± 50 seconds during the first week of placebo and 375 ± 50 seconds during the second week (P value not significant). The mean of these values for each patient was used for comparison with those obtained during nifedipine therapy. Exercise time averaged 471 ± 72 seconds at the 10 mg dose of nifedipine and 522 ± 78 seconds at the 20 mg dose. Exercise time was increased in eight of nine patients at the 10 mg dose. A significant difference was seen by use of analysis of variance ($P < 0.005$). Both 10 mg and 20 mg doses of nifedipine caused increases (both $P < 0.05$) in exercise time when compared with that obtained during placebo administration. Exercise time did not differ when the 10 mg and 20 mg doses were compared (P value not significant).

Maximal S-T segment shift averaged 1.83 ± 0.3 with placebo, 1.73 ± 0.2 at 10 mg dose of nifedipine and 1.59 ± 0.2 at the 20 mg dose. Analysis of variance did not show any difference among these groups (P value not significant).

The product of heart rate and systolic blood pressure with the patient standing at rest before starting exercise was $95.21 \times 10^2 \pm 6.65 \times 10^2$ during the period of placebo administration, $96.90 \times 10^2 \pm 5.57 \times 10^2$ during administration of 10 mg of nifedipine, and $89.60 \times 10^2 \pm 5.10 \times 10^2$ at the 20 mg dose. There was no significant difference among these values. The product of heart rate and systolic blood pressure just before end-exercise averaged $200.18 \times 10^2 \pm 12.02 \times 10^2$ during placebo administration, $204.66 \times 10^2 \pm 9.06 \times 10^2$ with 10 mg of nifedipine and $220.23 \times 10^2 \pm 14.46 \times 10^2$ after 20 mg of nifedipine. Four of the nine subjects showed a consistent increase in this product at both doses of nifedipine compared with that during placebo administration. The Friedman test showed no significant difference among these groups. These findings did not change when comparisons were limited to only those patients who ended exercise because of angina during both placebo and nifedipine treatment.

Resting blood pressure and heart rate: Standing systolic blood pressure after administration of either placebo or nifedipine averaged 129.8 ± 3.6 mm Hg 3 hours after placebo, 121.8 ± 4.8 mm Hg 3 hours after 10 mg of nifedipine and 118.6 ± 4.7 mm Hg 2.4 hours after 20 mg of nifedipine. A nonrandom grouping of data was observed ($P < 0.05$). Systolic blood pressure at the 20 mg

dose of nifedipine was significantly lower than that with placebo (P <0.05). However, systolic pressure after administration of 10 mg of nifedipine did not differ from that with placebo, and the effect of 10 or 20 mg of nifedipine on systolic pressure did not differ either. Diastolic blood pressure averaged 85.7 ± 2.4 mm Hg with placebo, 79.0 ± 3.0 mm Hg after 10 mg of nifedipine and 79.2 ± 5.0 after 20 mg of nifedipine. These values showed nonrandom grouping (P <0.05). Comparison of individual diastolic blood pressure pairs revealed no significant differences, although the values with 20 mg of nifedipine versus those with placebo almost reached statistical significance (P <0.1).

Standing heart rate averaged 73.2 ± 4.4 beats/min 3 hours after placebo, 76.9 ± 3.7 after 10 mg of nifedipine and 78.7 ± 3.5 after 20 mg of nifedipine. There was no significant difference among these groups.

Treadmill exercise response during double-blind evaluation: Table I gives results of treadmill exercise tests performed during the double-blind portion of the study. Exercise duration increased significantly (13 percent) with nifedipine therapy, whereas maximal S-T shift during exercise, pre-test standing and peak product of heart rate × systolic blood pressure did not differ significantly. Analysis of the individual data revealed a consistent decrease in heart rate × systolic blood pressure product at a given work load until maximal exertion after nifedipine therapy. Small decreases in both heart rate and systolic blood pressure at a given exercise level contributed to the decreases in the double product.

Discussion

These results of the single-blind comparison of 10 and 20 mg of nifedipine versus placebo indicate that this drug is a very promising agent for the treatment of stable angina pectoris due to atherosclerotic coronary artery disease. Nifedipine, 10 and 20 mg, caused a 37 and 44 percent decrease, respectively, in the number of anginal episodes per week, when compared with those with placebo.

Similarly, weekly nitroglycerin consumption decreased progressively with increasing nifedipine doses. The 10 mg dose of nifedipine caused a 47 percent lessening in nitroglycerin use, compared with that with placebo, and the 20 mg dose caused a 53 percent decrease. Treadmill exercise time showed a corresponding rise (28 percent increase after 10 mg of nifedipine and 42 percent increase at the larger dose). Four patients ended exercise primarily because of fatigue or dyspnea after drug therapy, with angina no longer being the limiting factor.

TABLE I

Treadmill Exercise Results in Nine Subjects During Double-Blind Comparison of Nifedipine and Placebo

	Placebo	Nifedipine
Exercise duration (sec)	462.29 ± 51.73	523.5 ± 49.15*
Maximal S-T shift (0.1 mI)	1.77 ± 0.26	1.60 ± 0.22†
Pre-test HR × SBP ($\times 10^{-2}$)	98.85 ± 3.98	96.75 ± 3.98†
Maximal HR × SBP ($\times 10^{-2}$)	216.2 ± 10.07	213.46 ± 8.80†

* P (probability) <0.005 compared with placebo value.
† P value not significantly different compared with placebo value.
HR = heart rate; SBP = systolic blood pressure.

Limitations of study: Potential objections to these results include the relatively small number of patients studied and the possibility that the single-blind administration of active drug may not have adequately hidden the knowledge of when nifedipine was being given. Also, placebo therapy given during weeks 1 and 2 might itself cause a decrease in symptoms, and serial exercise tests (as performed during weeks 1, 2, 4 and 6) may result in prolonged exercise duration merely as a result of familiarization with the procedure. During the single-blind portion of the study, the data did not show a significant increase in exercise time during placebo therapy alone (from week 1 to week 2), nor did placebo decrease the rate of anginal attacks. However, during the double-blind phase, exercise times while the patient was receiving placebo were increased compared with the times obtained while placebo was given during single-blind evaluation, suggesting that serial exercise by itself caused increased duration. Despite this, the four patients who received placebo after nifedipine during double-blind evaluation showed decreased exercise time compared with that during therapy with nifedipine. The findings are in accord with the experience of other investigations previously performed in both a single- and double-blind manner.[14,15]

Mechanisms of nifedipine effects: Our data confirm previous work showing that nifedipine lowers resting systolic blood pressure without causing much reflex increase in heart rate.[14] During the treadmill testing, the product of systolic blood pressure and heart rate at peak exercise did not differ significantly from that with placebo after nifedipine therapy. This product correlates highly with myocardial oxygen consumption during exercise in normal subjects and, under controlled conditions, is reproducible for individual patients with angina pectoris.[17,18] Although experimental evidence in conscious laboratory animals and in man at rest has shown nifedipine to increase coronary blood flow.[11,19] the present data, together with those of other studies,[19] do not support a primary increase in coronary blood flow and myocardial oxygen consumption during exercise as the mechanism for improving treadmill exercise duration. The data do indicate that nifedipine lengthens the time required to reach the peak product of blood pressure and heart rate. Therefore, as with nitrates, a peripheral effect of this drug may be responsible for the observed increase in exercise tolerance.[20] Further investigation of nifedipine and other calcium antagonists will be necessary to determine definitely whether myocardial oxygen consumption and coronary blood flow during exercise are enhanced or whether perfusion of potentially ischemic areas is improved.[21,22]

Effect of Nifedipine on Myocardial Ischemia: Analysis of Collateral Flow, Pulsatile Heat and Regional Muscle Shortening

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Effects of intravenous nifedipine on the ischemic myocardium of dogs subjected to coronary ligation were evaluated with a newly developed myothermal technique. Sensitive, fast-reacting miniature thermistors implanted within the ventricular wall were used in conjunction with low noise thermistor bridges to monitor beat-to-beat intramyocardial heat pulses and to detect intramyocardial cold transients after mechanized injections of cold saline into the left atrium. Myocardial ischemia reduced the amplitude of the pulse signals and decreased mean intramyocardial temperature. Ischemia also reduced the amplitude of the intramyocardial cold transients detected after injection of cold saline solution. All thermal changes due to ischemia were partly reversed by nifedipine. The amplitude of the cold signals correlated positively ($r = 0.85$) with local myocardial perfusion estimated by the radioactive microsphere technique. Thus, estimates of local perfusion by two independent techniques confirmed that nifedipine increased collateral perfusion. In addition, simultaneous measurements of peripheral coronary pressure indicated that the drug decreased resistance in the coronary bed distal to the occlusion. Ultrasonic measurements of myocardial segment length revealed that nifedipine improved myocardial shortening in ischemic zones, a response that accounts for the nifedipine-induced increases in local heat. Thus, the results show that nifedipine increases collateral flow to the acutely ischemic myocardium and that improved perfusion is accompanied by enhanced contractile performance. These findings also indicate that the protective action of nifedipine on ischemic myocardium is not predominantly mediated by a cardioplegic effect limiting the metabolic needs of the myocardium at risk.

In previous studies[1] with isolated rabbit hearts perfused at low flow, we demonstrated that nifedipine not only prevents the development of ischemic contracture and the accumulation of mitochondrial calcium but also promotes the recovery of contractile function after reperfusion. We further showed[2] that nifedipine exerts a protective effect on the globally ischemic canine heart subjected to hypothermic cardiopulmonary bypass. In other experiments[3] we found that in conscious dogs subjected to sudden complete coronary occlusion, continuous infusion of nifedipine in a nonhypotensive dosage increases collateral perfusion and diminishes ischemic injury.

In the present study, the mechanism of action of nifedipine on the perfusion of the acutely ischemic canine myocardium was evaluated using the microsphere technique. In addition, experiments were designed to determine whether increases in collateral flow are accompanied by improvements in local myocardial performance or whether nifedipine, like verapamil,[4] selectively depresses ischemic myocardium.

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Methods

Flow measurements with radioactive microspheres and electromagnetic transducers: Large dogs weighing between 52 and 68 kg were used for the hemodynamic experiments. The dogs were anesthetized with halothane, intubated, ventilated under positive pressure with room air and subjected to left thoracotomy. Blood gases were monitored with a blood gas analyzer (Instrumentation Laboratory, model 213), and arterial pH and gas tensions were maintained within the following ranges: pH, 7.35 to 7.45; partial pressure of oxygen (PO_2), 95 to 115 mm Hg; and partial pressure of carbon dioxide (PCO_2), 35 to 45 mm Hg. The pericardium was opened and the left anterior descending coronary artery ligated proximal to the takeoff of a major diagonal branch, as schematically illustrated in Figure 1. A Silastic® catheter (2.13 mm outside diameter; 1.0 mm inside diameter) connected to a Statham P23Db pressure transducer was inserted into the left anterior descending coronary artery distal to the ligation to monitor peripheral coronary arterial pressure. A small electromagnetic flow probe (lumen size 0.5 to 1.5 mm; Narco-Bio-Systems, series 721 "C") connected to a digital electromagnetic flowmeter (Narcomatic model RT-500) was fitted around the diagonal branch to monitor flow (Fig. 1). Small branches of the left anterior descending coronary artery 10 to 13 mm distal to the occlusion, and branches of the diagonal artery between its takeoff from the left anterior descending coronary artery and the flow probe were tied. Thus, in this preparation anterograde diagonal branch flow was supplied exclusively by retrograde flow in the left anterior descending coronary artery, as indicated by the arrows in Figure 1.

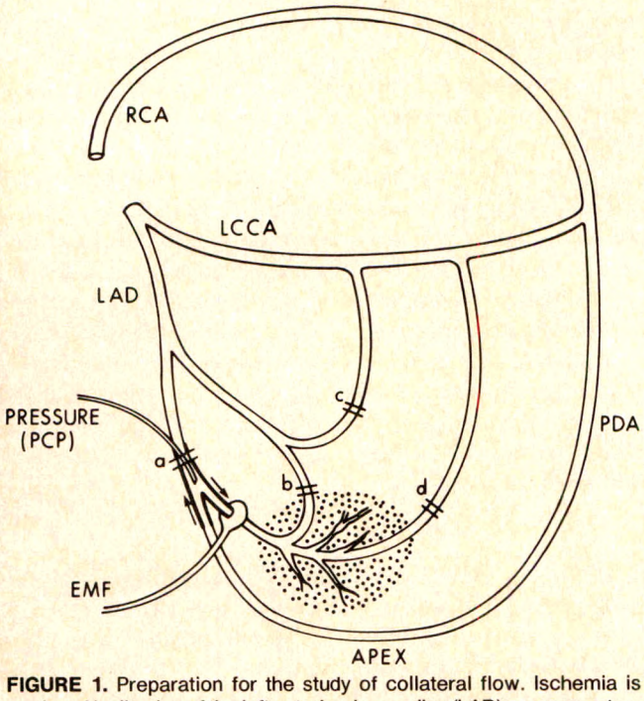

FIGURE 1. Preparation for the study of collateral flow. Ischemia is produced by ligation of the left anterior descending (LAD) coronary artery distal and close to a diagonal branch (**site a**). Large superficial collaterals (**b, c and d**) potentially contributing to the perfusion of the ischemic zone are ligated. Peripheral coronary pressure (PCP) is monitored downstream from the occlusion of the left anterior descending coronary artery. Flow in the diagonal branch is detected with a small electromagnetic flow (EMF) probe. The left anterior descending coronary artery downstream from the occlusion and the diagonal branch between the left anterior descending coronary artery and the flow probe are dissected free (**heavy lines**) to make sure that anterograde electromagnetic flow in the branch is supplied exclusively by retrograde left anterior descending coronary artery flow as indicated by the two arrows. LCCA = left circumflex coronary artery; PDA = posterior descending coronary artery; RCA = right coronary artery.

Prominent superficial anastomoses potentially contributing to the perfusion of the myocardium in the distribution area of the diagonal branch were ligated. Such anastomoses occur between diagonal branches of the left anterior descending coronary artery or between diagonal and marginal branches of the circumflex coronary artery (Fig. 1). These additional ligations were performed in an attempt to increase the dependence of the perfusion of the ischemic zone on anterograde diagonal branch flow. Zero diagonal branch flow was obtained by transient occlusion downstream from the implanted flow probe. In 7 of 16 preparations, a satisfactory electromagnetic signal demonstrating forward diastolic flow was recorded. Dogs in which a stable signal of diastolic forward flow was not recorded were used for another project. Catheters connected to Statham pressure transducers were inserted into the left ventricular cavity and ascending aorta, and an electromagnetic flow probe was placed around the ascending aorta to monitor cardiac output.

In addition to monitoring peripheral coronary pressure and diagonal branch flow, estimation of regional coronary flow was performed with use of carbonized microspheres, 15 ± 3 μm in diameter, labeled with strontium-85, cerum-141, and chromium-51 (3M Company). For each flow measurement, approximately 1.5 to 2.0 × 10^6 microspheres in 1 ml of detergent-free saline solution were injected through an implanted left atrial catheter during withdrawal of an arterial reference sample from the aortic catheter as previously described.[3] Myocardial blood flow was calculated from the formula $Q_M = Q_A \times (C_M/C_A) \times 100$, in which Q_M = myocardial perfusion in ml/min per 100 g fresh myocardium, Q_A = rate of arterial withdrawal in ml/min, C_A = total radioactivity in disintegrations/min recovered in the arterial withdrawal and C_A = radioactivity in disintegrations/min per g of fresh myocardium.[3]

The effect of nifedipine on collateral flow was studied in a three part experiment: In part 1, a first microsphere injection was administered 60 minutes after occlusion of the left anterior descending coronary artery to determine the extent of the ischemia before pharmacologic intervention. *In part 2,* a second microsphere injection was given 3 minutes after the onset of treatment with nifedipine to evaluate acute effects of the drug on myocardial perfusion. An initial intravenous loading dose of nifedipine, 3 μg/kg, was administered slowly over a 2 minute period, followed by a maintenance infusion of 0.5 μg/kg per min. *In part 3,* a third dose of microspheres was given after ligation of the diagonal branch to characterize the dependence of local myocardial perfusion on anterograde diagonal branch flow. Three sites in the distribution area of the diagonal branch exhibiting the most intense cyanosis were identified, and the dogs were then killed with an overdose of anesthetic agent.

Transmural cylindrical tissue samples were cut from the ventricular wall with a no. 12 cork borer (19 mm inside diameter) and halved into an endocardial and an epicardial portion as previously described.[3] Samples were obtained from the identified sites of ischemia and from the nonischemic left lateral wall. Radioactivity of the radionuclides in the samples was measured with a germanium-lithium detector.[3]

Measurements of myocardial temperature with thermistors: In this series of experiments, myothermal measurements were performed with specially designed ul-

trafast-reacting thermistors and low noise thermistor bridges, essentially as described by Berger et al.[5] The thermistors were beads made of copper oxide-free materials, hermetically sealed in glass and aged. The diameter of the final units was approximately 0.5 mm. The resistance of the thermistors ranged between 20 and 50 kohm, and their response time was between 3 and 6 msec. The flexible leads of the thermistors were Teflon®-covered, multistrand steel wires covered with Silastic tubing. The performance of the low noise alternating current lock-in amplifier bridges (IBT Laboratories, Rockville, MD) has previously been described in detail.[5] For these experiments, we constructed a triple differential thermistor bridge with which temperatures at three different sites, and temperature differences between these sites, could be monitored simultaneously. The outputs of the thermistor bridges were monitored on an oscilloscope (Tektronix, model 7313). To calibrate and test the linearity of the instrumentation immediately before use, the thermistors were immersed in temperature-controlled water baths.

Open chest dogs weighing between 20 and 31 kg were prepared as described earlier. An occlusive snare was fitted around the left anterior descending coronary artery distal to the first major diagonal branch. To implant thermistors, the myocardium was superficially cut with a no. 12 gauge intravenous needle. The thermistor catheters were inserted through the superficial cut and pressed downward to position their tips within the inner layer of the ventricular wall. The flexible leads of the thermistors were immobilized on the surface of the heart by means of superficial no. 5–0 silk sutures. At the end of some experiments, the myocardium surrounding the implanted thermistor was excised for histologic study. Light microscopic examination of six samples revealed a rim of injury of about 0.5 mm and little or no hemorrhage.

Intramyocardial thermistors were implanted at two sites: (1) the lateral wall distant from the area of cyanosis produced during brief occlusion of the left anterior descending artery, and (2) the anterior wall where cyanosis was maximal. An additional thermistor was placed in the ascending aorta.

Two types of thermal experiments were conducted. In one set of experiments, semiquantitative assessment of local myocardial perfusion was performed applying Rein's Thermo-Stromuhr principle.[6] With a power injector (Columbus Instruments International Corp., model 500), 3 ml of saline solution at room temperature was injected through an implanted catheter into the left atrium. These cold injections into the central circulation produced temperature transients in the aorta and, with some delay, at the two myocardial sites. To examine whether intramyocardial thermal transients could serve as an index of local myocardial perfusion, signals were compared with local flow measurements based on the microsphere technique described. Microspheres labeled with different radionuclides were injected through a second left atrial catheter immediately before and after power injections of saline solution. At the end of the experiment, the position of the thermistors within the ventricular wall was accurately determined. Transmural cylindrical tissue samples centered around the thermistor sites were excised with a no. 12 cork borer. The subendocardial halves of the tissue samples surrounding the thermistors were used to measure radioactivity and to compute flow. Unfortunately, the use of the microsphere technique as a "gold standard" of local perfusion is not without shortcomings; sequential measurements in open chest dogs are known to exhibit considerable variation.[3,7,8] In the present experiments, measurements before and after power injection of saline solution differed by no more than 21 percent. The two sequential flow measurements with the microsphere technique were averaged for evaluation of the intramyocardial cold signals.

In another series of experiments, cold injections were serially administered before occlusion of the left anterior descending coronary artery, 2 minutes after occlusion and after slow intravenous administration of nifedipine (3 μg/kg) 4 minutes after occlusion. Changes in aortic temperature were used as reference signals (see later). In additional experiments, the instrumentation was used to record beat to beat fluctuations of temperature within the myocardium. This was possible for the first time because of the stability and sensitivity of the thermistor bridges and because of the small thermal mass and time constant of the thermistors. Mean and pulsatile myocardial temperatures before and after occlusion of the left anterior descending coronary were continuously monitored. Ten minutes after occlusion, the effects of intravenous nifedipine, 3 μg/kg, were evaluated.

Measurements of the length of the myocardial segment with ultrasonic transducers: These experiments were performed in open chest dogs weighing between 24 and 32 kg, prepared as described earlier. The instrumentation for ultrasonic measurements was assembled in our laboratory according to the specifications of Franklin.[9,10] During temporary occlusion of the left anterior descending coronary artery, ischemic and nonischemic sites of the left ventricular wall were delineated on the basis of the distribution of cyanosis. Subsequently, pairs of piezoelectric crystals measuring 2 mm in diameter were implanted 10 mm apart in the subendocardial layer of the ventricular wall in potentially ischemic and nonischemic zones. The crystals were connected to a four channel ultrasonic amplifier system. The instrument generated voltages proportional to the transit time of impulses traveling between the piezoelectric crystals, thus providing electric signals proportional to the distance between the crystals.[9,10] Changes in segment length and their first time derivatives were monitored with a fiberoptic recorder (Honeywell, model 1858). After stabilization of the monitored variables, the left anterior descending coronary artery was occluded. Two minutes after occlusion, a continuous intravenous infusion of nifedipine at a rate of approximately 1 μg/kg per hour was started and continued for the rest of the experiment. In other experiments serving as controls, no nifedipine was administered.

Statistical evaluation: The significance of the difference between sequential mean values in the same group was evaluated by the *t* test for paired samples.

Results

Flow measurements with radioactive microspheres and electromagnetic transducers: Figure 2 is a representative phasic record of the peripheral coronary pressure and anterograde diagonal branch flow in response to systemic administration of nifedipine (3 μg/kg). The drug produced a modest decrease in left ventricular and aortic pressure. Concomitantly, there was a prominent decline in peripheral coronary pressure whereas the electromagnetically measured flow increased, indicating reduced coronary resistance. Hemodynamic results are summarized in Table I. Nifedipine produced expected systemic hemodynamic changes, including an increase in heart rate, a decrease in arterial pressure and an increase in cardiac output. There was a significant decrease in mean peripheral coronary pressure and a significant increase in anterograde diagonal branch flow. Accordingly, total coronary

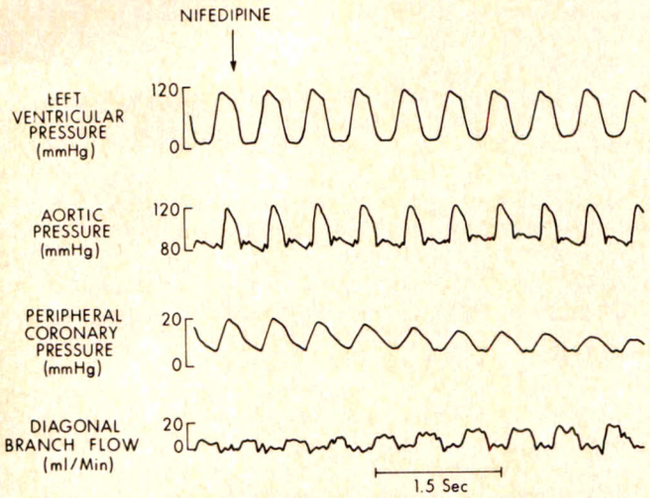

FIGURE 2. Effect of nifedipine on peripheral coronary pressure and branch flow (open chest dog). Phasic tracings and electromagnetic flow through the diagonal branch. Note that during the administration of nifedipine peripheral coronary pressure decreases whereas diagonal branch flow increases. Concomitantly, there is a modest decrease in aortic pressure.

TABLE 1

Systemic and Coronary Hemodynamic Responses to Nifedipine (0.5 μg/kg per min After an Intravenous Loading Dose of 3 μg/kg)

	Control	After Nifedipine
Heart rate (min^{-1})	129 ± 9	135 ± 13
Mean aortic pressure (mm Hg)	104 ± 6	89 ± 5*
Cardiac output ($ml \cdot kg^{-1} \cdot min^{-1}$)	122 ± 12	162 ± 18*
Mean peripheral coronary pressure (mm Hg)	16 ± 2	10 ± 1*
Mean diagonal branch flow (ml/min)	2.8 ± 0.19	3.6 ± 0.32*
Mean diagonal branch resistance ($mm\ Hg \cdot ml^{-1} \cdot min$)	5.7 ± 0.5	2.8 ± 0.2*

* Significantly different from control value (*t* test for paired samples; *P* (probability) <0.05).

Peripheral coronary arterial pressure and simultaneous electromagnetic flow in diagonal branch distal to the occluded left anterior descending coronary artery were monitored before (control) and after the administration of nifedipine. Values are mean ± standard error (no. = 7 dogs).

resistance in the vascular bed supplied by the diagonal branch was decreased.

Figure 3 summarizes the results of the three part coronary flow experiments using microspheres. The upper panel shows that, in comparison with control flow levels (part 1), perfusion was increased in tissue samples from nonischemic zones by administration of nifedipine both before (part 2) and after (part 3) ligation of the diagonal branch flows. In the distribution area of the diagonal branch, initial flow (part 1) was depressed, reflecting the ischemia induced by occlusion of the left anterior descending coronary artery and ligation of superficial collaterals as illustrated in Figure 1. During administration of nifedipine (part 2), collateral perfusion increased, a finding that is in accord with the

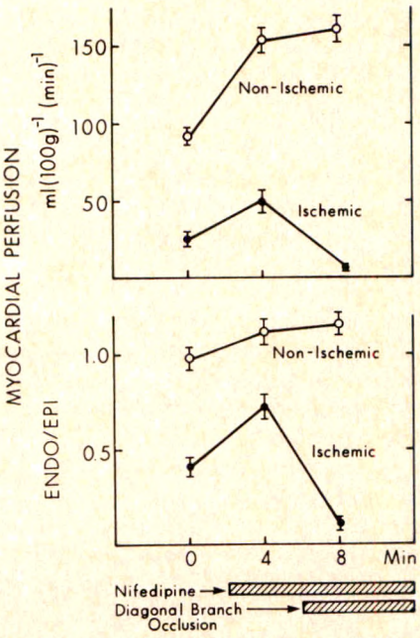

FIGURE 3. Diagram of the effects of nifedipine on collateral flow. The three consecutive points of each line represent the three parts of the experiment (see Fig. 2). Experiments were performed in seven dogs, and each dog contributed three samples to the data points. Vertical limits denote ± standard error. The three sequential values in the ischemic zone (●—●) and the first and second values in the nonischemic zone (O—O) are significantly different (*t* test for paired samples; $P < 0.05$). ENDO/EPI = endocardial/epicardial.

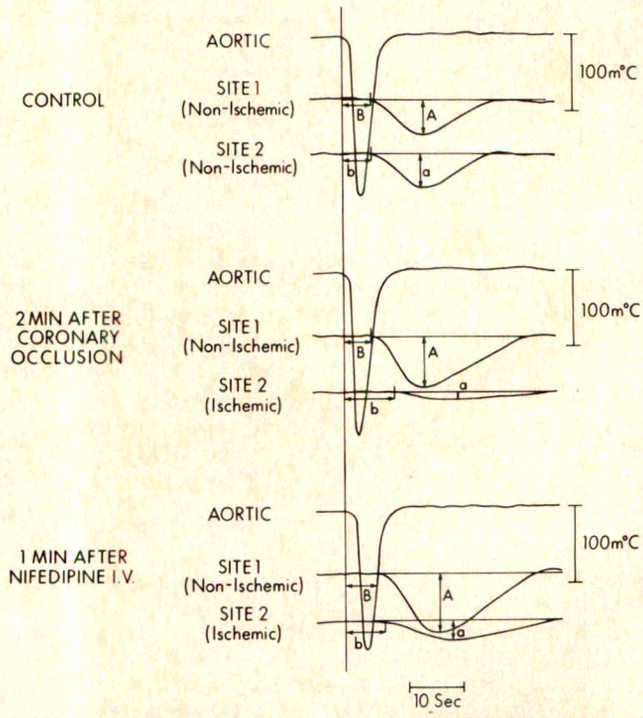

FIGURE 4. Cold transients in aorta and myocardium after injection of cold saline solution into the left atrium. Under control conditions (**top panel**) signals at the two myocardial sites are similar. After coronary occlusion (**middle panel**), the signal at ischemic site 2 is markedly attenuated (decreased amplitude a) and delayed (prolonged interval b). Intravenously (I.V.) given nifedipine (**bottom panel**) partly corrects the ischemic changes.

TABLE II

Cold Transients in Nonischemic and Ischemic Myocardium After Injection of Cold Saline Into the Left Atrium

	Peak Amplitude (μ° C/m$^\circ$ C sec)*			Aortomyocardial Delay (sec)		
	Control	Occlusion	Occlusion + Nifedipine	Control	Occlusion	Occlusion + Nifedipine
Site 1 (nonischemic)	62 ± 5	82 ± 8†	137 ± 15‡	2.91 ± 0.12	2.81 ± 0.13	2.72 ± 0.18
Site 2 (ischemic)	59 ± 3	14 ± 2†	20 ± 3‡	2.83 ± 0.16	9.17 ± 0.63†	7.01 ± 0.65‡

* Units for cold signal peak amplitude are explained in the legend for Figure 5.
† Value after occlusion significantly different from control value.
‡ Value after nifedipine (3 μg/kg intravenously) significantly different from value after occlusion and before treatment (*t* tests for paired samples; $P < 0.05$).
Values are mean ± standard error (no. = 7 dogs).

electromagnetic diagonal branch flow measurements described. However, after occlusion of the diagonal branch, during continued administration of nifedipine (part 3), perfusion was markedly decreased, demonstrating that most of the collateral flow to these zones was supplied by anterograde diagonal branch flow. In other words, part 3 of the experiment rules out the possibility that nifedipine-induced increases in collateral perfusion were predominantly contributed by channels other than the diagonal branch. Therefore, nifedipine-induced increases in collateral flow cannot be attributed to the opening of collateral vessels supplied by a pressure head other than that measured at the takeoff of the diagonal branch. Because diagonal branch flow increased in the presence of a decreased peripheral coronary pressure (part 2), we may conclude that the resistance in the vascular bed supplied by the diagonal branch decreased under the influence of nifedipine. The bottom panel of Figure 3 illustrates the concomitant changes in transmural flow distribution. Changes in transmural flow were apparently accompanied by relative increases in endocardial perfusion, a phenomenon that was particularly prominent in the ischemic zone.

Measurements of myocardial temperature with thermistors: In one series of experiments, saline solution at room temperature was mechanically injected into the left atrium, and temperatures were then sensed in the aorta and at two myocardial sites, one of which could be made ischemic. The top panel of Figure 4 shows that after saline injection, a cold transient was first detected in the aorta and, with some delay, at the two myocardial sites almost simultaneously. The middle panel shows that occlusion of the left anterior descending coronary artery produced a decreased (amplitude a) and a delayed (time interval b) signal in the ischemic zone whereas the amplitude of the signal in the nonischemic zone was increased. The negative and positive slopes of the signals reflecting the speed of cooling and rewarming differed greatly.

The bottom panel of Figure 4 depicts the effects of nifedipine on the cold signals after an identical injection of cold saline solution. Although the aortic cold transient was decreased reflecting the nifedipine-induced increase in cardiac output, the amplitudes of the signals at the nonischemic and ischemic sites were increased. In addition, compared with the middle tracing obtained before administration of nifedipine, the aortomyocardial delay (time interval b) was shortened for the ischemic zone. The experiments illustrated in Figure 4 are summarized in Table II. It can be seen that nifedipine-induced decreases in the aortomyocardial delay and increases in the amplitude of the cold signals in ischemic zones were reproducible.

To ascertain whether cold signals correlated with local myocardial perfusion, the cold signals were compared with myocardial perfusion measurements with the microsphere technique as described in the Methods section. Multiple variables derived from the time-temperature records were related to microsphere flows in methodologic studies. The peak amplitude of the intramyocardial cold signals was found to be one of the variables that correlated best with flow measurements by the microsphere technique (Fig. 5). Results shown in Figure 5 suggest that the thermal signals are quantitatively related to local myocardial perfusion.

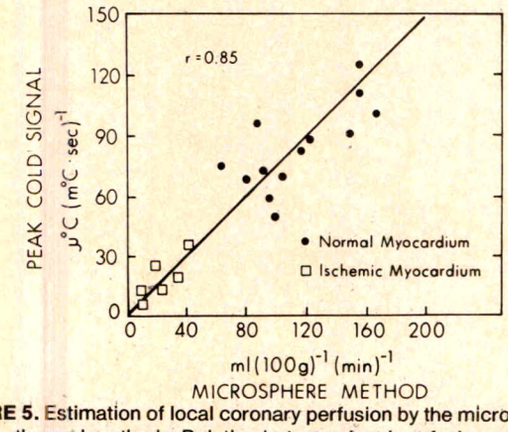

FIGURE 5. Estimation of local coronary perfusion by the microsphere and the thermal methods. Relation between local perfusion using the microsphere method (**abscissa**) and the thermal method (**ordinate**). Microsphere flows are expressed in ml/100 g per min and thermal flows in μ° C/m$^\circ$ × sec. The latter units were obtained by dividing the peak amplitude of the intramyocardial cold signals (in μ° C) by the aortic temperature-time integral (in m$^\circ$ C × sec). These units normalize the intramyocardial signal for the magnitude and duration of the cooling of the aortic blood entering the coronary ostium. μ° = microdegrees; m$^\circ$ = millidegrees.

Figure 6 is a representative tracing of beat-to-beat temperature fluctuations monitored before and after coronary occlusion. Under control conditions (top left panel), peak temperatures at the two myocardial sites were recorded early in diastole; this was probably related to the fact that heat released by muscular contraction took some time to be conducted to the thermistors. The delay is clearly not related to the responsiveness of the instrumentation, which, as mentioned before, was very fast compared to the physiologic events under study.[5] After coronary occlusion (top right panel), the amplitude and maximal positive slope of the pulsatile signal at the ischemic site decreased. Later during ischemia (bottom left panel), the signal at the ischemic site declined further and exhibited a markedly depressed maximal rate of temperature rise (dT/dtmax). In addition, the tracing showed a phase shift, temperature minima being now nearly simultaneous with the maxima recorded at the nonischemic site. After the administration of nifedipine (bottom right panel), the mean temperature increased, as indicated by the upward displacement of the tracing. Furthermore, the amplitude and maximal rate of temperature rise increased, and the phase shift was abolished. Results of experiments performed are summarized in Table III.

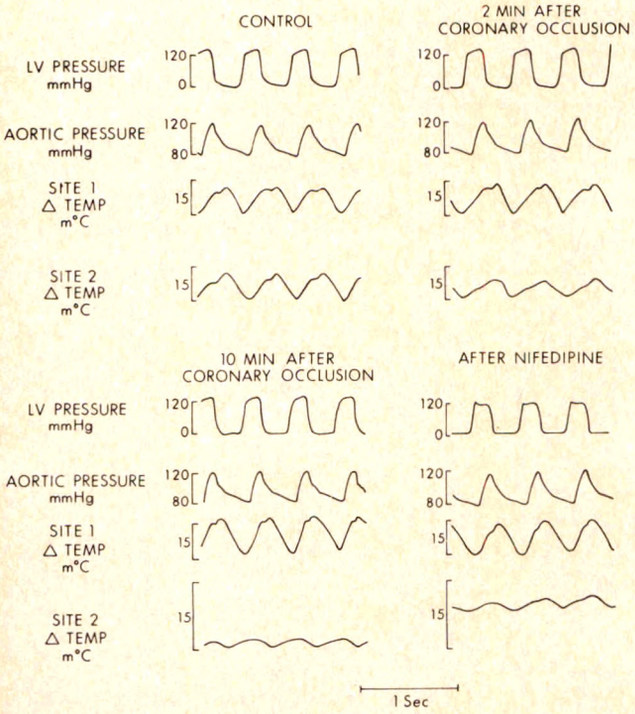

FIGURE 6. Recording of intramyocardial pulsatile temperature in nonischemic (site 1) and ischemic (site 2) myocardium (conscious dog). **Top left panel,** preocclusion control. **Top right and bottom left panels,** 2 and 10 minutes after left anterior descending coronary artery occlusion. **Bottom right panel,** after intravenous administration of nifedipine (3 μg/kg). Sites 1 and 2 are the nonischemic and ischemic intramyocardial sites, respectively. For description of tracings, see text. LV = left ventricular.

Measurements of myocardial segment length with ultrasonic transducers: Figure 7 is a representative tracing of the effects of nifedipine on myocardial shortening in an ischemic zone. After coronary occlusion, the segment fails to shorten during early and mid systole and is elongated at the end of both systole and diastole. Infusion of nifedipine partly corrects these typical ischemic changes. Results of the ultrasonic experiments are described in Table IV.

Discussion

Nifedipine and collateral flow: This study confirms earlier observations[3] that nifedipine increases collateral flow to the ischemic myocardium in dogs subjected to coronary occlusion. That collateral perfusion is not fixed but may be augmented by pharmacologic interventions is of considerable importance since improved perfusion may potentially limit the extent of ischemic injury.[3] The regulation of collateral perfusion in the ischemic canine myocardium is still incompletely understood.[11] Among mechanisms that may augment collateral flow are: (1) increased perfusion pressure acting on the collaterals, (2) decreased vascular resistance at the level of collaterals supplying the ischemic bed, and (3) decreased vascular resistance at the level of the ischemic bed itself. Results of the present study demonstrate that flow in a coronary arterial branch distal to a coronary occlusion increased in the presence of decreased perfusion pressure, consistent with a drop in vascular resistance. The increase in collateral flow occurred via the hypotensive coronary arterial system, as evidenced by the fact that ligation of the branch distal to the occlusion completely abolished the drug-induced increase in collateral flow. However, the present experiments do not differentiate between a fall in vascular resistance related to vasodilation and one due to decreased external compression of the vascular bed

TABLE III

Intramyocardial Pulsatile Heat Before and After Occlusion

	Peak Amplitude (m° C)	Peak dT/dt (m°C/sec)	Δ Mean T (m° C)
Site 1 (nonischemic)			
Control	15 ± 0.2	68 ± 5	0
Occlusion	18 ± 0.3*	131 ± 11*	+150 ± 16*
Occlusion + nifedipine	17 ± 0.4*	125 ± 12*	+141 ± 18*
Site 2 (ischemic)			
Control	14 ± 0.3	65 ± 7	0
Occlusion	3 ± 0.3*	18 ± 2*	−245 ± 26*
Occlusion + nifedipine	5 ± 0.5*†	25 ± 3*†	−186 ± 23*†

* Significantly different from control value at the same site.

† Value after nifedipine (3 μg/kg intravenously) significantly different from value after occlusion before treatment (*t* tests for paired samples; $P < 0.05$).

Peak amplitude in millidegrees (m° C) is the difference between maximal and minimal temperatures of pulsatile temperature tracing. dT/dt in a m° C/sec is the maximal positive slope of the temperature tracing. Δ mean T refers to the change in mean temperature (m° C) compared to the control value. Values are mean ± standard error (no. = 7 dogs).

(extracoronary component of coronary resistance). Unfortunately, the extracoronary component of coronary resistance is very difficult to evaluate in vivo.

Nifedipine and myocardial perfusion and performance: In this study, a myothermal technique was applied to assess myocardial perfusion and performance. To evaluate perfusion, intramyocardial temperature transients after bolus injections of cold saline into the left atrium were recorded. The sudden temperature decrease in the blood perfusing the myocardium was sensed outside the vessels, a method that has features in common with Rein's Thermo-Stromuhr.[6] Concomitant measurement of local perfusion using the microsphere technique revealed that the cold signals were related to local flow in a semiquantitative manner. During ischemia, when little blood reached the area surrounding the thermistor, diminutive cold signals were recorded. These ischemic signals were changed to a more normal pattern by the administration of nifedipine, a finding that agrees with the known effects of the drug on collateral perfusion. Although this technique does not provide precise measurements of local perfusion, it appears to have a potential for the rapid screening of the effects of multiple drugs on collateral flow. For the evaluation of myocardial performance, pulsatile and mean intramyocardial temperatures were monitored before and after coronary occlusion. Ischemia was associated with a decrease in mean temperature and produced characteristic changes in the pulsatile temperature tracings. The administration of nifedipine during ischemia raised the mean temperature and partly normalized the pulsatile temperature tracings. Under physiologic conditions, the temperature of aortic blood is always substantially lower than that recorded within the myocardium, and heat generated by the cardiac muscle is dissipated by myocardial perfusion.[12] Accordingly, nifedipine-induced increases in the mean temperature of ischemic zones under increased collateral flow suggest an increase in the heat liberated by the myocardium. This interpretation does not support the view that nifedipine, an agent known to exert negative inotropic effects in vitro,[1,3] selectively inhibits the activity of the ischemic myocardium, as has been reported for verapamil.[4]

Nifedipine and regional myocardial shortening: In the present experiments regional myocardial shortening was monitored using an ultrasonic technique developed by Theroux et al.[9] Depending on the severity of the ischemia, ischemic segments exhibited decreased systolic shortening or paradoxic systolic elongation. After administration of nifedipine, shortening during left ventricular ejection was improved, and in some segments paradoxic systolic elongation reverted to shortening. Increased contractile work in ischemic segments would be expected to be associated with increased heat production, in agreement with the myothermal measurements.

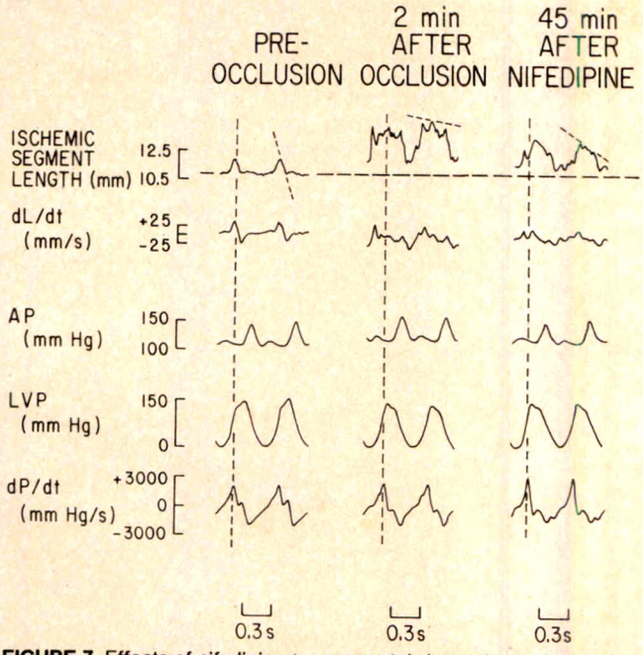

FIGURE 7. Effects of nifedipine on segmental shortening in the central ischemic zone. Before occlusion (**left panel**), segmental shortening and elongation occur mainly during early systole and early diastole, respectively. Note that there is systolic shortening throughout the period of ventricular ejection (**short dotted line at top of tracing**). Two minutes after occlusion (**middle panel**), the segment paradoxically elongates during early systole and remains long throughout ventricular ejection (**horizontal dotted line at top of tracing**). During subsequent treatment with nifedipine for 45 minutes (**panel on the right**), the ischemic pattern is largely corrected. Both minimal and maximal lengths are shorter compared with values 2 minutes after occlusion, and shortening takes place during systole. AP = aortic pressure; dL/dt = rate of segmental length change; dP/dt = first time derivative of left ventricular pressure; LVP = left ventricular pressure.

TABLE IV

Regional Myocardial Shortening Using Ultrasonic Method

	Control	Occlusion	Occlusion + Nifedipine
Segment length*			
EDL (mm)	12.07 ± 0.09	13.42 ± 0.04†	12.09 ± 0.04‡
ESL (mm)	10.52 ± 0.05	12.90 ± 0.03†	11.28 ± 0.03‡
ΔL (mm)	1.54 ± 0.01	0.51 ± 0.003†	0.08 ± 0.005‡
Peak LVP (mm Hg)	142 ± 6	138 ± 8	134 ± 6‡
LVdP/dt (mm Hg/sec)	2823 ± 141	2429 ± 311†	2407 ± 320
Heart rate (min^{-1})	140 ± 8	140 ± 8	143 ± 9

* Segment length measured in the central ischemic zone.
† Value 2 minutes after occlusion significantly different from control value.
‡ Value after subsequent treatment with nifedipine (1 μg/kg/hr for 45 minutes) significantly different from value 2 minutes after occlusion (*t* tests for paired samples; $P < 0.05$). In five dogs given no nifedipine the ischemic pattern of segmental shortening persisted 3 hours after coronary occlusion (data not tabulated). Values are mean ± standard error (no. = 5 dogs). EDL = end-diastolic length; ESL = end-systolic length; LVdP/dt = first derivative of left ventricular pressure; LVP = left ventricular pressure.

Implications: Our experimental results demonstrate that nifedipine-induced augmentation in collateral flow reflects a decreased total coronary vascular resistance in the low pressure coronary bed distal to the occlusion. Enhanced myocardial perfusion is accompanied by increased myocardial performance as assessed by measurements of myocardial temperature and shortening. In previous experiments we demonstrated that nifedipine decreased ischemic injury in conscious dogs subjected to coronary occlusion.[3] The present results demonstrate that preservation of ischemic myocardium does not occur at the expense of myocardial performance. Thus, the protective action of nifedipine on ischemic myocardium is not predominantly mediated by a cardioplegic effect limiting the metabolic needs of the myocardium at risk. Rather, as previously suggested,[3] improved perfusion appears to be the most important factor in limiting the extent of ischemic injury.

Acknowledgment

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Nifedipine: A Myocardial Protective Agent

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The effectiveness of the calcium antagonist nifedipine in preserving postischemic myocardial function and structural integrity was experimentally demonstrated in isolated rabbit hearts, in conscious dogs subjected to myocardial infarction, in open chest anesthetized dogs with normothermic regional ischemia induced for 1 to 2 hours and in dogs undergoing hypothermic global ischemia for 2 hours followed by 2 hours of reperfusion. Nifedipine had a beneficial effect on postischemic myocardial stiffness and mitochondrial calcium accumulation, which were correlated. Administration of nifedipine at the onset of myocardial infarction increased blood flow to ischemic zones of myocardial infarction and resulted in less loss of creatine kinase. It reduced by two- to three-fold the volume of the ischemia-reperfusion injury induced by left anterior descending coronary arterial occlusion and release and preserved indexes of hemodynamic function. Nifedipine was found effective in protecting myocardial performance and structure after 2 hours of global ischemia during hypothermic cardiopulmonary bypass. It is suggested that this agent may be useful as an adjunct to cold cardioplegia in man for enhanced myocardial protection during cardiac surgery.

The concept of chemical cardioplegia is not new. In 1955, Melrose et al.[1] demonstrated in animals and patients that a hyperkalemic, hyperosmolar ionic solution rapidly arrested the heart permitting a motionless surgical field when the aorta was cross-clamped. Reports by many surgeons followed,[2–6] cautioning against use of Melrose's solution because of late postoperative cardiomyopathy. The reports of Reidemeister et al.,[7] Kugelberg[8] and Kirsch et al.[9] in Europe and that of Gay and Ebert[10] in the United States stimulated new investigations of the efficacy and safety of chemical cardioplegia during clinical cardiac surgery. Clinical usage is now widespread.

Our investigations of the biochemical and ultrastructural patterns of the ischemia-reperfusion injury led to the idea that myocardial preservation might be improved by altering the abnormal membrane transport processes that occurred during ischemia. The rationale for our experiments was that by prevention of the accumulation of intracellular calcium, the consequent stiffness and decrease in contractility associated with ischemic injury and reperfusion could be ameliorated. To this end, a calcium antagonist, nifedipine, was chosen for investigation. This agent is known to be a calcium antagonist and is a potent vasodilator. Its mechanisms of action have not been fully delineated.

This study summarizes our past experimental experiences with nifedipine in modifying hemodynamic performance during ischemia, myocardial infarction and the ischemic-reperfusion injury associated with global ischemia during cardiopulmonary bypass. These data have been published previously,[11–13] and the reader is referred to these reports for details of the methods and results not covered in summarized form.

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Methods

Four preparations have been used: (1) isolated perfused rabbit hearts, (2) closed chest conscious dogs subjected to myocardial infarction, (3) open chest dogs with occlusion of the left anterior descending coronary artery for various time periods, and (4) global myocardial ischemia using cardiopulmonary bypass at 28° C.

Isolated perfused rabbit hearts: Albino rabbits weighing between 2.0 and 2.5 kg were used. Hearts were isolated and perfused in a retrograde manner at 37° C through the aorta. The perfusate contained (millimolar) sodium chloride, 118; potassium chloride, 2.8; potassium phosphate, 1.2; calcium chloride, 2.5; magnesium sulfate, 1.2; sodium bicarbonate, 25; and glucose, 5. After equilibration at 37° C with a gas mixture of 5 percent carbon dioxide–95 percent oxygen, the pH of the perfusate was 7.38. The rate of perfusion was maintained at 22 ml/min with a roller pump. A latex balloon mounted around a micromanometer was inserted into the left ventricular cavity for measurement of left ventricular pressure and its first derivative (dP/dt). The balloon was filled slowly with deaerated saline solution with use of a micrometer syringe until end-diastolic pressure stabilized between 5 and 8 mm Hg. A bipolar electrode was attached to the right ventricular wall and the heart was paced at a frequency of 180 beats/min. Thus, the major determinants of cardiac performance, namely, ventricular preload, afterload, heart rate, coronary flow and temperature were controlled.

All hearts were equilibrated for 30 minutes at a flow rate of 22 ml/min. Then a slow perfusion was started at the rate of 0.2 ml/min with the perfusate containing nifedipine or its vehicle and maintained for 60 minutes. Nifedipine or its vehicle was infused with a syringe pump into the perfusion system at a rate not exceeding 1 percent of the total flow. The calcium content of the myocardial mitochondrial fraction was determined using copper as a mitochrondrial marker.

Protection of ischemic myocardium by nifedipine in conscious dogs: Mongrel dogs were anesthetized with pentobarbital sodium (25 mg/kg), intubated and placed on a volume ventilator and had a left thoracotomy through the fifth left intercostal space. The left anterior descending coronary artery was dissected and a balloon occluder passed around it. Catheters were inserted into the left atrium, jugular vein and central aorta and an electromagnetic flow probe was placed around the aorta. The free ends of the transducer cables, snare and catheters were exteriorized dorsally at the base of the neck. The chest was closed and each animal was allowed to recover for 11 to 17 days. The hemodynamic measurements were made in conscious, loosely restrained dogs while they were lying quietly on the right side. Regional coronary blood flow was estimated by the microsphere method with carbonized microspheres, labeled with strontium-85, cerium-141 and chromium-51. After control data were obtained, the left anterior descending coronary artery was occluded. Twenty-nine minutes after occlusion an initial injection of microspheres was given and the administration of nifedipine or its vehicle was begun. Drug-treated animals received a loading dose of nifedipine of 5 μg/kg followed by a continuous intravenous infusion of the drug. A second injection of microspheres was given 3 minutes after the onset of the infusion of the drug or its vehicle and hemodynamic monitoring was continued for 3 hours. In four control and four treated animals an injection was administered at the end of the 3 hour interval. Finally, an injection of microspheres was given 24 hours after the occlusion and the animal was killed. Creatine kinase (CK) activity levels as well as radioactivity in core samples were determined for three zones of the myocardium: the nonischemic zone, the peripheral ischemic zone and the central ischemic zone.

Regional ischemia in open chest dogs: Mongrel dogs were anesthetized, intubated and ventilated and had a left thoracotomy. Catheters were placed through the groin vessels to the level of the right atrium and the ascending aorta. Two catheters were inserted into the left atrium, one of which was passed through the mitral valve into the left ventricle. Catheters were applied to strain gauge transducers and the phasic and mean pressures were recorded. An electromagnetic flow probe was applied to the ascending aorta for determination

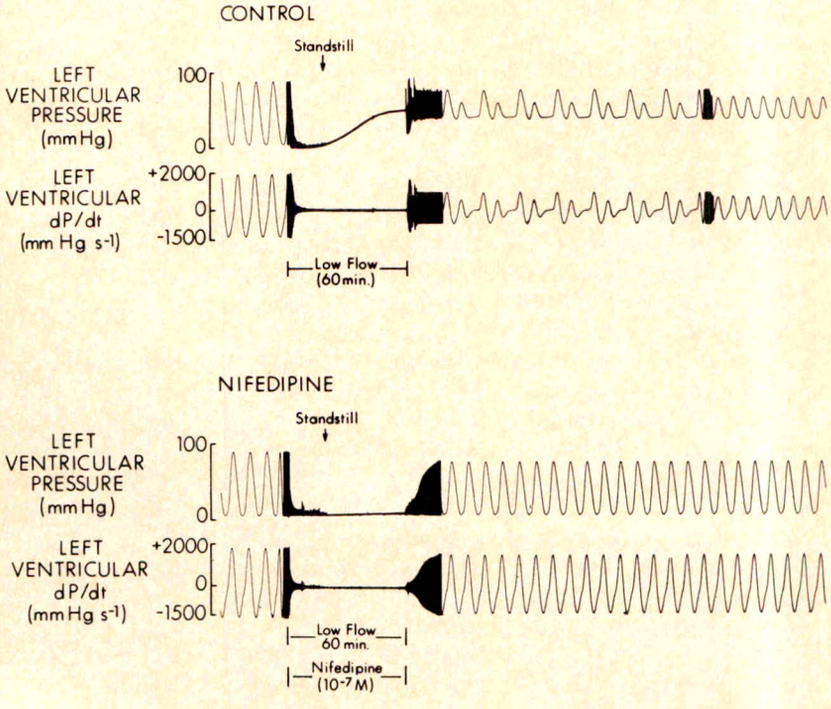

FIGURE 1. Inhibition of ischemic contracture by nifedipine during paced, isovolumic left heart experiments in the isolated perfused rabbit heart. Low flow refers to a rate of perfusion of 0.2 ml/min. Pre- and postischemic flow rates were 22 ml/min. s = second.

TABLE I

Calcium in Mitochondrial Fraction

Condition	Cases (no.)	Calcium (nanograms-atom/mg protein) Control	(no.)	Nifedipine (10^{-7} molar)
No perfusion	8	6.2 ± 0.3	8	6.3 ± 0.3
60 min high flow	7	7.6 ± 0.4	8	7.4 ± 0.4
60 min low flow	10	28.2 ± 1.9	10	8.0 ± 0.5
60 min low flow and 10 min of reperfusion	11	55.5 ± 4.8	12	10.0 ± 0.6

of phasic and mean flows. The left ventricular pressure was differentiated and recorded directly as left ventricular dP/dt. Occlusion of the left anterior descending coronary artery was accomplished with fine silicone rubber tubing. Animals were treated with nifedipine during the ischemic period of 1 or 2 hours' duration, during the 2 hour reperfusion period, which was constant for all animals, or during both periods. Each animal had an infusion of either saline solution or saline solution plus nifedipine at a rate of 40 ml/hour through an aortic root needle controlled by a Harvard infusion pump. The solutions were at room temperature and the dosage of nifedipine was 5 μg/kg per hour at an average concentration of 3.0 ± 0.3 mg/ml. Infusions were begun simultaneously with occlusion or release of the left anterior descending coronary artery. After 120 minutes of reperfusion, 100/mg per kg of colloidal carbon was injected through the left atrial catheter. After 5 minutes the heart was flushed and fixed in situ. The heart was cut with a calibrated slicer in slices approximately 5 mm thick, perpendicular to the apical-aortic root axis. After complete fixation each slice was photographed and the volume of the ischemic-reperfusion injury determined morphometrically; the results were expressed as a percent of total volume.

Global ischemia using cardiopulmonary bypass: Mongrel dogs were placed on total cardiopulmonary bypass with systemic hypothermia of 28° C, and topical cardiac hypothermia was produced with 4° C of Ringer's lactate. Each animal received substrate priming with insulin, glucose and potassium and osmolality was briefly raised with an infusion of 12.5 g of mannitol before clamping of the ascending aorta. Two hours of global ischemia was induced, after which each animal was reperfused for 30 to 60 minutes during normal sinus rhythm with an empty, beating nonworking heart. Each dog was weaned from bypass, if possible, and followed up for 2 hours. The experimental group received 5 μg/kg per hour of nifedipine through an aortic root catheter during ischemia. The control animals received the vehicle in an identical volume of 50 ml/hour. All data were statistically analyzed, and stroke work, cardiac index and total peripheral vascular resistance were calculated.

Results

Isolated perfused rabbit hearts: The initial effects of low flow of the perfusate at a rate of 0.2 ml/min resulted in a marked decline of developed left ventricular pressure and dP/dt in all hearts (Fig. 1). On reperfusion of the control hearts, peak pressure recovered to a level of 78 percent of preischemic values and these hearts recovered only 38 percent of preischemic values for peak dP/dt. The control hearts showed a marked elevation of the end-diastolic pressure to 40 mm of Hg. Rabbit hearts perfused with the same protocol and perfusate except for the addition of nifedipine, 10^{-7} molar, during the low flow period showed an 87 and 85 percent recovery of peak pressure and peak dP/dt, respectively. It is clear that the end-diastolic pressure increased only 2 mm Hg in contrast to 40 mm Hg for the control hearts (Fig. 1).

The mitochondrial calcium determinations (Table I) demonstrated that control values for calcium in units of nanograms-atom/mg protein for hearts perfused for 60 minutes with increased flow was 7.6 ± 0.4 (mean ± standard error of the mean). Hearts perfused under conditions of reduced flow for 60 minutes without the presence of nifedipine in the perfusate resulted in a calcium index of 28.2 ± 1.9 whereas those treated with nifedipine yielded a normal value of 8.0 ± 0.5. If 10 minutes of reperfusion was used after 60 minutes of reduced flow, the control and nifedipine-treated hearts had values of 55.5 ± 4.8 and 10.0 ± 0.6, respectively. The differences between control and treated hearts were statistically significant P <0.001 level. The relation

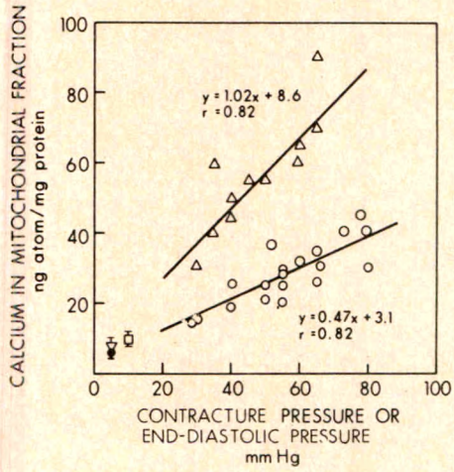

FIGURE 2. Relation between ischemic contracture and accumulation of calcium in mitochondrial fraction in perfused rabbit hearts. Mitochondrial fractions were prepared with solutions containing ruthenium red. **The closed circle** = after a standard equilibration period, hearts were perfused at 22 ml/min for 60 minutes with a buffer containing no nifedipine (no. = 7); **the reversed triangle** = perfusions at low flow (0.2 ml/min) for 60 minutes with a buffer containing nifedipine (10^{-7} M) and its vehicle (no. = 9); **the square** = after a 60 minute period of low flow with nifedipine, hearts were reperfused at 22 ml/min for 10 minutes with a buffer containing no nifedipine (no. = 10); **open circles** = 60 minutes of perfusions at low flow with a buffer containing a vehicle without nifedipine; **triangles** = 60 minutes of low flow with a buffer containing a vehicle without nifedipine followed by 10 minutes of reperfusion. r = correlation coefficient.

TABLE II

Systemic Hemodynamics in Eight Control and Nine Nifedipine-Treated Dogs

	Treatment	Control (before occlusion)	Time After Occlusion			
			29 Min	33 Min	3.5 Hours	24 Hours
Ventricular rate (beats/min)	None	80 ± 4	118 ± 5*	122 ± 5*	127 ± 6*	131 ± 8*
	Nifedipine	82 ± 4	117 ± 5*	148 ± 7*†‡	141 ± 7*‡	138 ± 8*
Mean aortic pressure (mm Hg)	None	96 ± 3	99 ± 3	97 ± 3	100 ± 4	98 ± 4
	Nifedipine	97 ± 3	98 ± 3	93 ± 3*†‡	96 ± 5	96 ± 5
Cardiac output (ml/kg per min)	None	104 ± 3	131 ± 8*	127 ± 8	141 ± 10*	138 ± 8*
	Nifedipine	106 ± 4	132 ± 7*	177 ± 11*†‡	172 ± 9*‡	169 ± 7*‡
Mean left atrial pressure (mm Hg)	None	4 ± 0.6	5 ± 0.6	5 ± 0.8	6 ± 0.8*	7 ± 0.7*
	Nifedipine	4 ± 0.5	4 ± 0.6	3 ± 0.5*†‡	4 ± 0.5	4 ± 0.6‡

Values are expressed as mean ± standard deviation.
* Significantly different ($P < 0.05$, t test for paired samples) from control value immediately before coronary occlusion.
† Significantly different ($P < 0.05$, paired t test) from preceding values.
‡ Value in the treated group significantly different ($P < 0.05$, t test for unpaired samples) from the value in the control group at the same time after occlusion.

between cardiac mechanics and calcium in the mitochondrial fraction is shown in Figure 2.

Protection of ischemic myocardium by nifedipine in conscious dogs: The hemodynamic data are summarized in Table II. Treatment with nifedipine induced modest and transient decreases in aortic and left atrial pressures and significant increases in the heart rate 33 minutes and 3 1/2 hours after coronary occlusion. Cardiac output was significantly increased at all times in dogs given nifedipine in comparison with animals that did not receive this drug. Cardiac output was increased by 39 percent 33 minutes after coronary occlusion and by 22 percent 3 1/2 and 24 hours after occlusion.

Data for blood flow to the endocardium and epicardium are shown in Table III. Blood flow was increased by nifedipine in all flow zones except the small central core of the infarction. The percent increases were similar for endocardium and epicardium, ranging from 20 to 73 percent.

Myocardial CK activity level in international units/g wet weight 24 hours after myocardial infarction was similar in the nonischemic zone for both the placebo- and nifedipine-treated dogs (2,064 ± 27 versus 2,103 ± 25, respectively). In the peripheral ischemic zone (11 to 30 ml/min per 100 g), the CK activity level was 418 ± 22 to 631 ± 39 in the placebo group versus 1,083 ± 60 to 1,748 ± 86 in the nifedipine-treated dogs. In the central ischemic zone (less than 10 ml/min per 100 g), the control value was 206 ± 16 versus 301 ± 22 for drug-treated dogs. The relation of CK activity to morphometric infarction is shown in Figure 3.

Regional ischemia in open chest dogs: The preliminary studies of regional ischemia used left anterior descending arterial occlusion for 1 or 2 hours and reperfusion for 2 hours in 19 control and 35 nifedipine-treated dogs. Control animals had a stroke work index for 9.6 ± 1.6 g-m/m^2 2 hours after release of the ligature. In contrast, dogs that received nifedipine during the ischemia and reperfusion intervals had a stroke work index of 19.1 ± 1.6 g-m/m^2, which was statistically similar to the preischemic mean value for all animals. The rate of increase of left ventricular pressure (dP/dt) was 2,294 ± 93 and 3,125 ± 288 mm Hg sec ($P < 0.01$) for control and treated dogs, respectively. The left ventricular end-diastolic pressure in control dogs was increased by 39 percent in comparison with treated dogs at the termination of the experiment.

Use of nifedipine resulted in a reduction of injury volume of 140 percent (4.8 ± 0.9 to 2.0 ± 1.1 percent) after 1 hour of ischemia and 2 hours of reperfusion. Animals given nifedipine during 2 hours of ischemia and 2 hours of reperfusion had a threefold reduction in injury volume, from 8.9 ± 1.9 to 3.1 ± 0.8 percent.

Global ischemia with cardiopulmonary bypass: None of the seven control animals could be weaned from cardiopulmonary bypass after 2 hours of ischemia at 28° C with a saline infusion at room temperature during the ischemic period. All had a marked loss of stroke work

TABLE III

Endocardial and Epicardial Blood Flow in Eight Control and Nine Nifedipine-Treated Dogs—24 Hours After Occlusion

Flow Range (ml/min per 100 g)	Endocardium			Epicardium		
	Control	Treated	%Δ	Control	Treated	%Δ
>65	128 ± 2.6	198 ± 7.8	55	109 ± 2.1	168 ± 2.8	54
31–65	82 ± 6.8	122 ± 8.9	48	72 ± 3.0	103 ± 5.9	43
21–30	45 ± 3.1	78 ± 5.5	73	39 ± 2.2	67 ± 3.9	72
11–20	32 ± 1.9	46 ± 2.9	43	28 ± 2.7	40 ± 3.8	43
<10	5 ± 0.5	6 ± 0.7	20	5 ± 1.1	6 ± 1.5	20

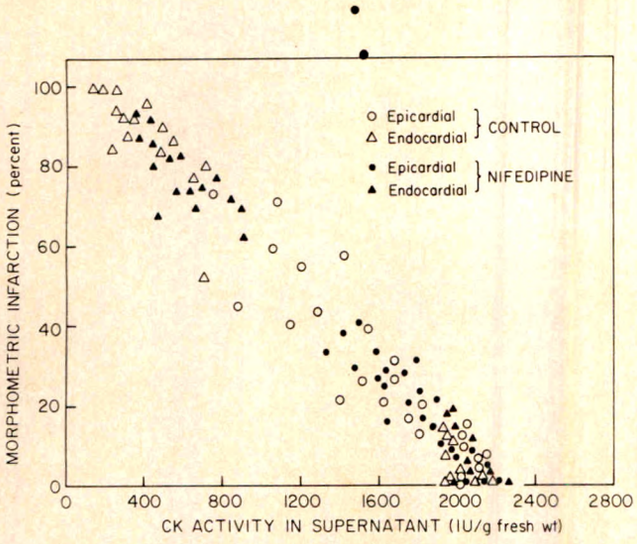

FIGURE 3. Relation between creatine kinase (CK) activity in supernatant fraction and morphometric infarction in corresponding samples in conscious dogs. The correlation coefficients (r) for the four different data sets were: **open circles** = epicardial control (no. = 25):$r = 0.91$; **open triangles** = endocardial control (no. = 25):$r = 0.99$; **closed circles** = epicardial treated dogs (no. = 25): $r = 0.83$; **closed triangles** = endocardial treated dogs (no. = 25): $r = 0.99$.

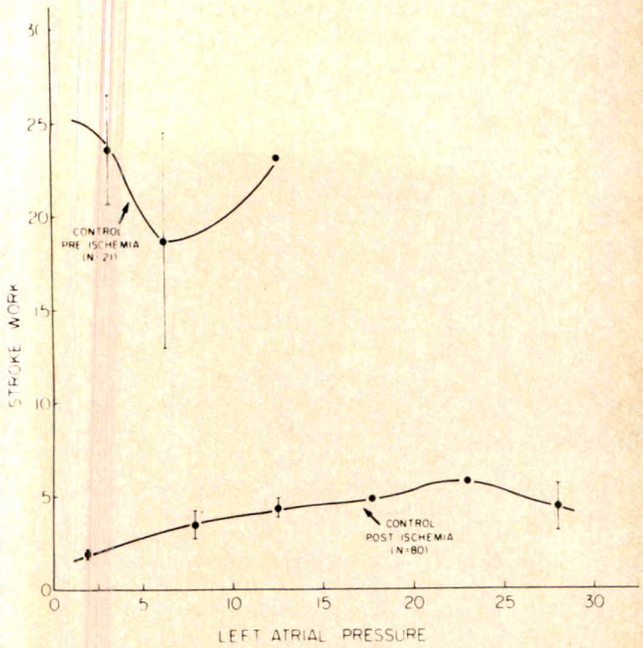

FIGURE 4. Relation of left ventricular stroke work (g-m/m^2) and left atrial pressure (mm Hg) for seven control dogs before and after 2 hours of global ischemia at 28° C and 2 hours of reperfusion at 37° C. Note the flat response to volume loading after ischemia and reperfusion. N = number of measurements.

and left ventricular dP/dt, a reduction of 70 percent of cardiac output and no response to volume loading (Fig. 4). There was an 85 percent depression of stroke work and a 53 percent decrease in dP/dt. In marked contrast, the six animals receiving nifedipine during the 2 hours of global ischemia had a 27 percent reduction in cardiac output, a 17 percent reduction in stroke work and a 19 percent reduction in left ventricular dP/dt. (Fig. 5). A comparison of control and treated dogs is shown in Table IV. All treated animals were weaned from cardiopulmonary bypass and had a nearly normal response to volume loading (Fig. 6). Histologic studies revealed marked subendothelial injury in the control animals, whereas two thirds of the drug-treated hearts were judged normal.

Discussion

Four different experimental preparations were used: (1) isolated perfused rabbit heart, (2) the closed chest, awake dog, (3) the anesthetized open chest dog, and (4) the anesthetized open chest dog placed on total cardiopulmonary bypass at 28° C. Use of nifedipine in all four preparations demonstrated that this calcium flux antagonist increased blood flow to ischemic areas and reduced the hemodynamic consequences of the ischemic-reperfusion injury.

The isolated perfused rabbit heart experiments showed that nifedipine was effective in reducing post-

TABLE IV

Comparison of Mean Hemodynamic Values in Seven Control and Six Drug-Treated Dogs After 2 Hours of Global Ischemia

Determination	Control (no. = 7)	Drug-Treated (no. = 6)	P Value
LAP (mm Hg)	9.3	10	NS
HR (beats/min)	155	150	NS
LVP max (mm Hg)	87	140	<0.001
LVEDP (mm Hg)	14	7.7	<0.003
CVP (mm Hg)	9.6	7.3	<0.005
MAP (mm Hg)	64	90	<0.001
CO (liters/min)	700	1,320	<0.001
SV (ml/beat)	4.52	8.80	<0.001
SW (g-m)	3.34	9.9	<0.001
LV dP/dt (mm Hg/sec)	1,853	2,766	<0.005

CO = cardiac output; CVP = central venous pressure; HR = heart rate; LAP = left atrial pressure; LVEDP = left ventricular end-diastolic pressure; LV dP/dt = rate of rise of left ventricular pressure; LVP_{max} = maximal left ventricular pressure; MAP = mean arterial pressure; NS = not significant; P = probability; SV = stroke volume; SW = stroke work index.

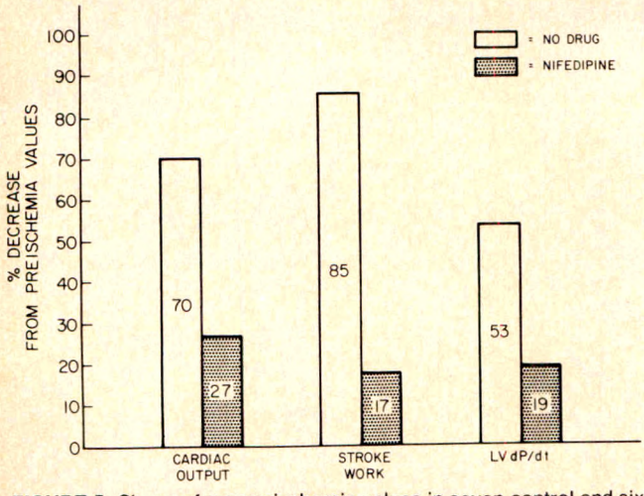

FIGURE 5. Change from preischemic values in seven control and six nifedipine-treated dogs for cardiac output, stroke work and left ventricular (LV) dP/dt. The differences between groups were statistically significant at a probability (*P*) value of <0.001 to 0.005.

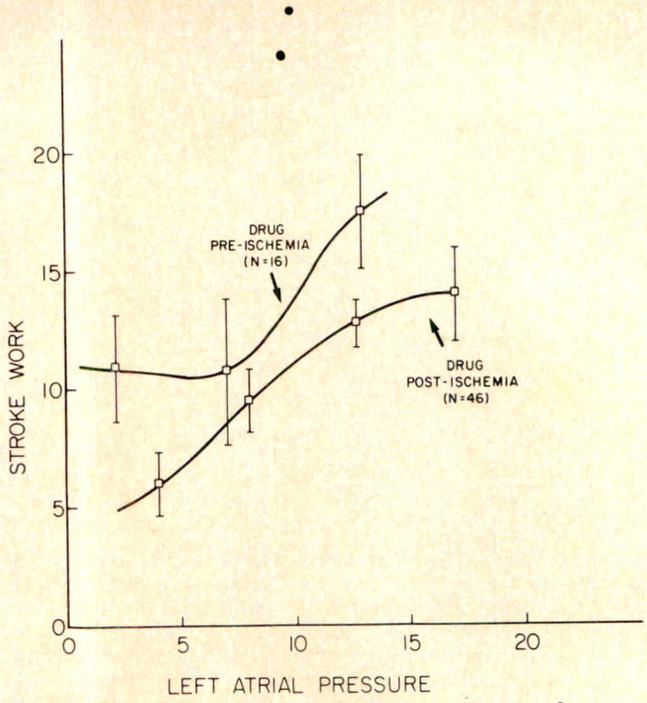

FIGURE 6. Relation of left ventricular stroke work (g-m/m^2) and left atrial pressure (mm Hg) for six nifedipine-treated dogs before and after 2 hours of global ischemia at 28° C and 2 hours of reperfusion at 37° C. Note the near normal response to volume loading after ischemia and reperfusion. N = number of studies.

ischemic mechanical impairment of the myocardium and prevented the elevation of left ventricular end-diastolic pressure. It also prevented an increase in mitochondrial calcium concentration. Increases in mitochondrial calcium were found to parallel the severity of myocardial contracture and the lack of diastolic relaxation after reperfusion.

The experiments in which myocardial infarction was induced in the awake dog demonstrated that nifedipine significantly increased blood flow to ischemic and nonischemic areas of the myocardium and decreased the characteristic abnormal distribution of blood flow associated with myocardial infarction. The increase in blood flow to the various flow zones correlated with the preservation of (K) activity in these areas.

The regional ischemia-reperfusion experiments demonstrated a preservation of hemodynamic function and a reduction in morphometrically determined injury volume. The preservation of myocardium was more marked with a longer period of ischemia.

The global ischemia experiments showed a potential practical method of enhancing myocardial protection during cardiac surgery. Although cardiac hypothermia during ischemia has been the principal method used for myocardial protection in the past, the injection of cold cardioplegic solutions into the aortic root at the initiation of global ischemia has resulted in a lesser incidence of perioperative left ventricular failure, myocardial infarction and death.[14–17]

Clinical implications: The clinical problem of postoperative left ventricular pump failure has continued. Some investigators have related the incidence of the postoperative low cardiac output syndrome to ischemic time or the complexity of the operation, or both.[16] Conti et al.[18] suggested that this complication is most closely related to the preoperative state of the myocardium.

It appeared to us that preservation of myocardium in the setting of cardiac surgery would be enhanced by specific biochemical and pharmacologic interventions in addition to hypothermia and rapid arrest with hyperkalemic solutions. Nifedipine was evaluated because of its pharmacologic action as an antagonist of calcium transport across the cell membrane. The experiments with global ischemia demonstrated that in a setting analogous to clinical practice, nifedipine conferred significant hemodynamic and histologic protection to the ischemic-reperfused myocardium. All nifedipine treated dogs were weaned from bypass without difficulty in contrast to the control dogs that could not sustain a cardiac output compatible with survival and had profound depression of other indexes of ventricular function. The results of all our experiments are highly consistent and show that nifedipine preserves hemodynamic function and biochemical cell integrity and ameliorates the morphometric and histologic injury associated with ischemia and reperfusion.

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Effects of Nifedipine After Intravenous and Intracoronary Administration

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A study with nifedipine, given intravenously or into the left coronary artery, was undertaken in an effort to distinguish the peripheral from the central effects of the drug in patients with stable angina. There was a significant antianginal effect 1 hour after intravenous administration of 1.0 mg of nifedipine. Intravenous administration of 0.1 mg of the drug had no antianginal effect, and did not cause hemodynamic alterations or influence coronary sinus oxygen saturation. Intracoronary infusion of 0.1 mg of nifedipine caused a significant increase in coronary sinus oxygen saturation that was abolished 5 minutes after the end of the infusion. A similar increase in oxygen saturation was found after intravenous administration of 1.0 mg of the drug; this effect, quantitatively somewhat smaller, also disappeared after 5 minutes. Infusion of 0.1 mg of nifedipine into the left coronary artery had an antianginal effect during exercise, documented by a reduction in the exercise-induced increase in left ventricular end-diastolic pressure and in the exercise-induced S-T segment depression. A similar antianginal effect, quantitatively slightly more pronounced, was achieved with intravenous administration of 1.0 mg of nifedipine.

It is concluded that the antianginal potency of nifedipine cannot be related to its effect on coronary arteriolar resistance because increased flow has returned to normal when the antianginal effect persists. The mechanism of action must include a direct cardiac influence, most likely on myocardial metabolism. No serious side effects were observed after intravenous or intracoronary administration of nifedipine.

The beneficial effects of nifedipine in patients with angina pectoris are well known. The agent benefits those with stable angina as well as those with the variant form of angina. Since the first studies in 1972[1–3] these favorable results have been repeatedly documented.[4,5]

Nifedipine was introduced as a coronary dilator, that is, an agent that increases coronary flow by reducing coronary arteriolar resistance.[6] In addition to this dilating effect on coronary arterioles, it produces dilatation of the large coronary arteries.[7] Under experimental conditions, the drug also exerts a negative inotropic effect on the myocardium by its calcium antagonistic properties.[8,9] In addition, its influence on peripheral circulation is well documented. This effect seems to be mainly directed toward the arterial system because the agent has only slight influence on the capacitance vessels.[10,11]

The following investigation was undertaken to compare the results of intravenous and intracoronary administration of nifedipine in an attempt to separate the peripheral and central effects of the drug.

Methods

Nifedipine administration: Nifedipine, 0.1 mg, was used in a solution of 1 ml alcohol. Nifedipine was infused with use of a motor-driven syringe at a rate adjusted to 1 ml over 2 minutes for the administration of 0.1 mg and to 10 ml over 2 minutes for the administration of 1.0 mg.

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Group I patients: Ten men with stable angina pectoris were studied with repeated exercise tests. Each patient had to perform an exercise test before and after intravenous infusion of 0.1 and 1.0 mg of nifedipine. The tests were performed according to the following protocol, with randomization to days 1 and 2.

Day 1
1. Exercise test before medication.
2. 30 minute recovery.
3. Intravenous infusion of 0.1 mg of nifedipine over 2 minutes.
4. 60 minute recovery.
5. Exercise test.

Day 2
1. Exercise test before medication.
2. 30 minute recovery.
3. Intravenous infusion of 1.0 mg of nifedipine over 2 minutes.
4. 60 minute recovery.
5. Exercise test.

The work load and duration of exercise were kept constant in all four tests. The S-T segment depression was quantitatively evaluated and compared, the sum of all S-T depressions before medication being taken as 100 percent. All patients had typical angina, and all showed typical ischemic S-T depression in the electrocardiogram during exercise. Severe coronary heart disease was documented with selective coronary arteriography (Table I).

Group II patients: Fifteen patients with different diagnoses were studied during left and right heart catheterization. After completing coronary arteriography and left ventriculography, the coronary sinus was catheterized with a USCI ventriculography catheter, no. 8 or with a fiberoptic catheter (American Optical Company). Nifedipine, 0.1 mg, was infused over a period of 2 minutes into the left coronary artery through a Sones catheter (no. 8F). Coronary sinus oxygen saturation was monitored until control levels were again reached. A second infusion of nifedipine, 1.0 mg, was given intravenously, and coronary sinus oxygen saturation was again monitored until control levels were reached.

Group III patients: Seven men with stable angina and typical ischemic S-T depression during exercise due to coronary heart disease documented with selective coronary arteriography and left ventriculography (Table I) were studied during left heart catheterization at rest and during exercise. After completing routine coronary angiography, the patients had a 25 minute recovery period. A first exercise test was performed with a previously determined work load and duration of exercise. After 30 minutes of recovery, 0.1 mg of nifedipine was infused into the left coronary artery; after an interval of 15 minutes the second exercise test was performed at an identical work load and for the same period of time. After 30 minutes of recovery, 1.0 mg of nifedipine was infused intravenously, and 15 minutes later the third exercise test was performed. Aortic and left heart hemodynamics and S-T segment changes in the electrocardiogram were monitored during and after exercise.

Group IV patients (control group): Five men with coronary artery disease served as control subjects. These men followed the same protocol used by patients in Group III but did not receive an infusion of nifedipine and did not undergo continued monitoring of left heart hemodynamics.

All patients from Groups I, III and IV had severe coronary artery disease, documented with selective coronary arteriography and left ventriculography (Table I). All had typical angina pectoris and had marked S-T depression in the electrocardiogram during and after exercise. Informed consent was obtained from all patients participating in the study.

Student's *t* test was used in the statistical analysis.

TABLE I

Results of Coronary Arteriogram and Left Ventriculogram in Patients of Group I, III and IV

Case no.	Age (yr)	Coronary Angiogram (% narrowing of luminal diameter) LMCA	LAD	LCx	RCA	LVEF (%)
		Group I				
1	58	—	100	80	80	40
2	57	40	100	80	100	51
3	46	—	70	30	0	80
4	58	—	40	—	90	72
5	53	—	80	30	100	55
6	62	20	80	50	100	70
7	48	—	—	95	10	72
8	46	—	60	85	—	81
9	65	40	80	70	100	68
10	52	—	100	40	40	74
		Group III				
11	63	20	—	90	80	69
12	43	80	—	30	—	73
13	65	40	80	70	100	68
14	47	30	70	100	60	71
15	64	10	60	60	30	69
16	48	0	30	90	100	59
17	59	0	100	30	30	74
		Group IV				
18	51	20	60	20	100	75
19	55	0	90	90	20	69
20	52	0	80	20	90	76
21	38	20	70	20	30	56
22	58	20	50	20	90	80

LAD = left anterior descending coronary artery; LCx = left circumflex artery; LMCA = left main coronary artery; LVEF = left ventricular ejection fraction; RCA = right coronary artery.

Results

Intravenous nifedipine: 0.1 versus 1.0 mg dose (Group I): The antiischemic potency of 0.1 and 1.0 mg of intravenous nifedipine was compared in 10 patients. In the exercise test after 0.1 mg of nifedipine, the mean S-T segment depression in the electrocardiogram during and after exercise was 110 percent; this value was not significantly different from the control value of 100 percent. After 1.0 mg of nifedipine, S-T segment depression was significantly reduced from 100 to 48 percent of the control value. The different responses to the smaller and larger dose are shown in Figure 1. The antiischemic activity of 1.0 mg of nifedipine given intravenously, which is suggested by this finding, was seen 60 minutes after intravenous application.

Intracoronary versus intravenous nifedipine (Group II): In 10 other patients the effects of nifedipine infused into the left coronary artery and of nifedipine infused intravenously were compared in respect to the alteration of coronary sinus oxygen saturation. To achieve a comparable cardiac effect, that is, an equipotent dose, a dose relation of 1:10 was arbitrarily chosen. A significant increase in oxygen saturation occurred after the 0.1 mg intracoronary infusion as well as after

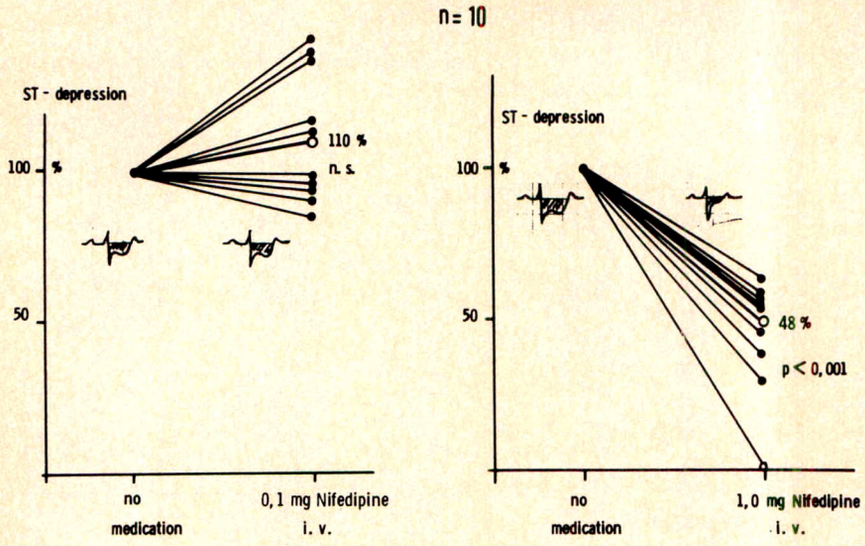

FIGURE 1. S-T depression during exercise is significantly reduced after an intravenous (i.v.) dose of 1.0 mg of nifedipine (**right**) whereas no significant difference is seen before and after the intravenous dose of 0.1 mg (**left**). One hundred percent (100%) represents the control amount of S-T depression. n = number of patients; n.s. = not significant; p = probability.

the 1.0 mg dose given intravenously. In five other patients of Group II no change was seen after intravenous infusion of 0.1 mg. The peak values of oxygen saturation were slightly higher after infusion of 0.1 mg of nifedipine into the left coronary artery than after the intravenous dose of 1.0 mg. Therefore, the intracoronary dose was slightly more than equipotent in relation to the 1.0 mg dose given intravenously (Fig. 2).

Hemodynamic variables were monitored during both interventions. Although no change could be seen after the infusion of 0.1 mg into the left coronary artery, the 1.0 mg intravenous dose led to a significant decrease in aortic and left ventricular end-diastolic pressure and to a significant increase in heart rate (Fig. 3).

Effect on hemodynamics (Group III): In seven patients with severe coronary heart disease hemodynamic variables were monitored during rest as well as during exercise tests performed with no medication, after infusion of 0.1 mg nifedipine into the left coronary artery and after intravenous infusion of 1.0 mg. In contrast to the values at rest, a significant decrease in left ventricular end-diastolic pressure during exercise occurred, even after the small intracoronary dose of nifedipine (Fig. 4, Table II). The rise in end-diastolic pressure provoked by exercise-induced ischemia could be abolished or diminished by the intracoronary administration of 0.1 mg of nifedipine, a dose that did not appear to affect the general circulation. Therefore, a

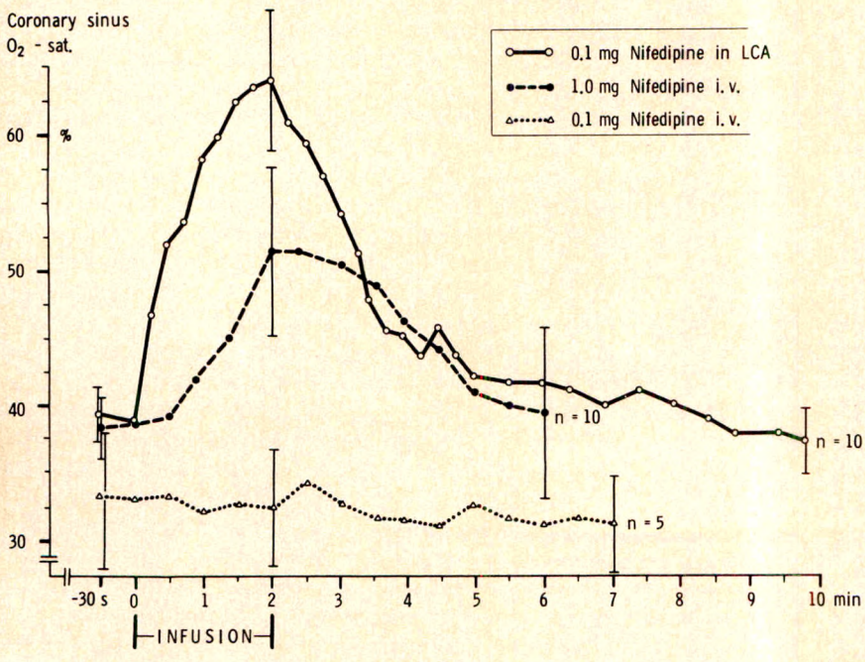

FIGURE 2. Oxygen saturation (sat.) in the coronary sinus during three different interventions: 1.0 mg infused intravenously (i.v.) and 0.1 mg infused into the left coronary artery (LCA) resulted in a significant increase in oxygen saturation, whereas 0.1 mg administered intravenously had no effect. Mean values with standard deviation are shown. n = no. of patients.

direct cardiac effect, which is at least partly responsible for the antianginal activity of this agent, must be postulated. In the exercise test performed after intravenous administration, a slightly more pronounced decrease in left ventricular end-diastolic pressure was observed, together with changes in systemic hemodynamics. Because the third exercise test was performed 1 hour after the intracoronary infusion of nifedipine it is possible that persistence of the effects of the intracoronary dose potentiated the effects of the intravenous dose.

In the same patients, S-T segment changes during exercise were monitored and quantitatively evaluated. A significant reduction in exercise-induced S-T segment depression was noted in parallel with the decrease in left ventricular end-diastolic pressure. The amount of S-T depression was reduced to 34 percent of control values after the intracoronary dose and to 21 percent after the intravenous dose (Fig. 5, Table II). The decreased S-T depression after intracoronary as well as after intravenous nifedipine was accompanied by a reduction in anginal pain.

Control (Group IV): In the control group of five patients neither systematic alteration in exercise-induced S-T depression nor anginal pain was observed (Fig. 5, Table III) when the three exercise tests performed in each patient were compared.

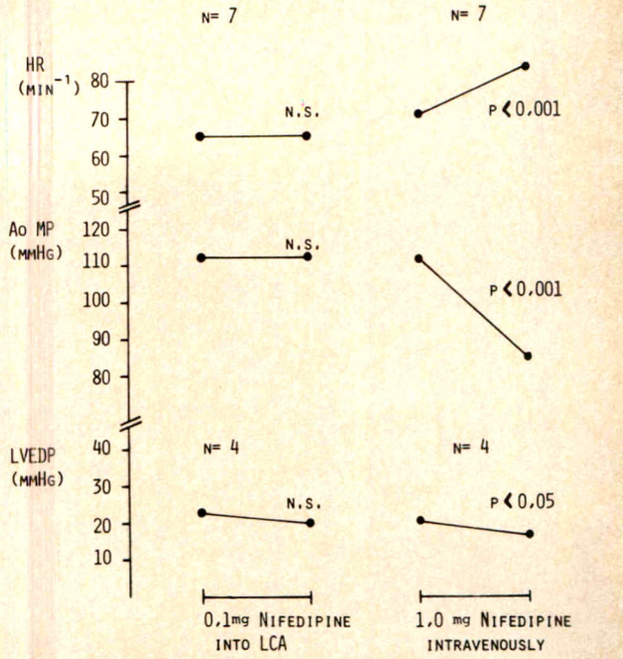

FIGURE 3. Hemodynamics at rest are unchanged after infusion of 0.1 mg of nifedipine into the left coronary artery (LCA); after intravenous infusion of 1.0 mg a significant decrease in aortic mean pressure (Ao MP) and left ventricular end-diastolic pressure (LVEDP) are evident, as well as an increase in heart rate (HR). N = number of patients; N.S. = not significant; P = probability.

Discussion

The antianginal action of nifedipine in patients with the variant form of angina as well as those with stable angina is well documented. The effect of the drug in patients with variant angina is thought to be due to its direct action on smooth muscle of the coronary arteries, thus relieving coronary arterial spasm. Although the latter mechanism is well understood, the mode of action in stable angina has not yet been clarified; it is even unknown whether the effect of nifedipine in stable angina is peripheral or central. This study was undertaken in an effort to distinguish peripheral from central effects of the drug.

Intravenous nifedipine: An intravenous dose of 1.0 mg of nifedipine was used. The antianginal action of this

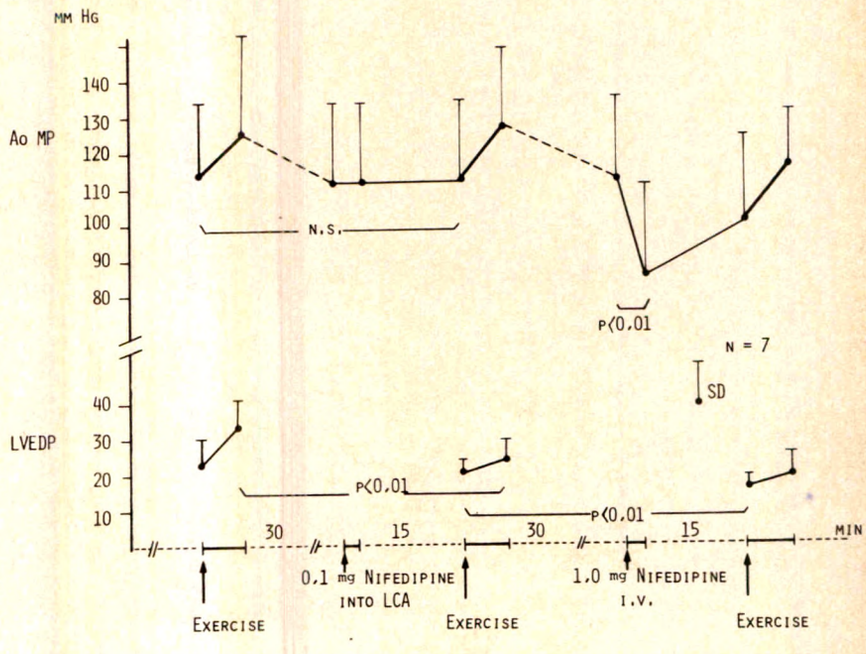

FIGURE 4. After infusion of 0.1 mg of nifedipine into the left coronary artery (LCA), during exercise there is a significant decrease in left ventricular end-diastolic pressure, indicative of an antianginal effect, that is, a reduction in an exercise-induced increase in end-diastolic pressure. After 1.0 mg given intravenously (i.v.), a decrease in exercise-induced increase in left ventricular end-diastolic and a reduction in aortic mean pressure (Ao MP) are evident. Ao MP = aortic mean pressure; N = number of patients; N.S. = not significant; P = probability; SD = standard deviation.

TABLE II

Group III. Hemodynamic Data and S-T Depression at Rest and During Exercise in Seven Patients With Stable Angina Studied Without Medication, After 0.1 mg of Nifedipine Infused Into the Left Coronary Artery and After 1.0 mg of Nifedipine Infused Intravenously

Case no.	First Exercise Test (control)								Second Exercise Test (0.1 mg Nifedipine into LCA)								Third Exercise Test (1.0 mg Nifedipine i.v.)							
	Heart Rate (min^{-1})		$\overline{AoP}$ (mm Hg)		LVEDP (mm Hg)		Sum of S-T↓		Heart Rate (min^{-1})		$\overline{AoP}$ (mm Hg)		LVEDP mm Hg		Sum of S-T↓		Heart Rate (min^{-1})		$\overline{AoP}$ (mm Hg)		LVEDP (mm Hg)		Sum of S-T↓	
	R	Ex	R	Ex	R	Ex	mv	%	R	Ex	R	Ex	R	Ex	mv	%	R	Ex	R	Ex	R	Ex	mv	%
11	76	118	112	127	—	—	21.6	100	70	105	112	117	—	—	11.3	52.3	94	111	110	109	—	—	7.9	36.6
12	57	91	104	96	19	31	14.4	100	57	109	104	120	20	22	0.2	1.4	69	104	92	112	15	16	0	0
13	67	86	100	108	—	—	6.3	100	61	86	100	104	—	—	3.8	60.3	74	91	96	104	—	—	4	63.5
14	68	133	124	134	15	22	20.7	100	68	138	126	128	15	16	10	48.3	75	122	92	110	12	14	3.2	15.5
15	83	111	158.	181	—	—	3.7	100	80	98	156	169	—	—	2	54.1	94	105	147	149	—	—	0.3	8.1
16	59	115	96.	120	26	36	20.9	100	60	103	88	136	20	28	2	9.6	46	100	72	112	18	28	3.5	16.7
17	56	83	104	112	30	40	12.1	100	56	83	96	112	25	27	4.7	33.9	62	81	88	108	18	18	1.7	14.0
no.	7	7	7	7	4	4	7		7	7	7	7	4	4	7		7	7	7	7	4	4	7	
Mean	66	105	114	125	22.5	32.3	14.2	100	65	103	112	127	20	23.3	4.8	37.1	73	102	100	115	15.8	19	2.9	22.1
SD	10.4	18.8	21.7	27.5	6.8	7.8	7.3	51	8.6	18.2	23	21.4	4.1	5.5	4.2	23.2	17.1	13.3	23.7	15.3	2.9	6.2	2.7	21.4
SEM	3.9	7.1	8.2	10.4	3.4	3.9	2.8	19	3.2	6.9	8.7	8.1	2.1	2.8	1.6	8.8	6.5	5	8.9	5.8	1.5	3.1	1.0	8.1

AoP = aortic mean pressure; Ex = during exercise; i.v. = intravenously; LCA = left coronary artery; LVEDP = left ventricular end diastolic pressure; R = at rest; SD = standard deviation; SEM = standard error of the mean; S-T↓ = S-T segment depression.

FIGURE 5. Exercise-induced S-T segment depression is reduced by intracoronary as well as by intravenous (I.V.) administration of nifedipine. One hundred percent (100%) represents the control value of S-T depression. LCA = left coronary artery; N = number of patients; P = probability.

dose was found to be comparable with that achieved in earlier studies with a sublingual dose of 20 mg. It is known that after sublingual administration the effect lasts for several hours. From the present study it can be derived that the antianginal activity of intravenous nifedipine continues for more than 1 hour.

Intracoronary nifedipine: role of increased coronary blood flow: This duration of effect is different from that on coronary blood flow. When nifedipine was infused into the left coronary artery or administered intravenously, there was a significant increase in coronary blood flow, as seen from coronary sinus oxygen saturation levels. This increased blood flow was short-lasting, with values returning to normal within 5 minutes after either the intracoronary or the intravenous dose. An infusion of 0.1 mg of nifedipine into the left coronary artery caused an even more pronounced increase in blood flow than did 1 mg of the drug infused intravenously. The effect of intravenous administration is in accord with early experimental results[6,7]; the similar effect after using the intracoronary route has not previously been reported.

From these findings we conclude that the antianginal potency seen 1 hour after application of nifedipine is not related to the short-lasting increase in total coronary blood flow. Because it is well known that increased blood flow, rather than ameliorating angina, can provoke it through a "steal" phenomenon, one can hardly assume that increased total coronary blood flow has a beneficial effect on angina. Lichtlen and co-workers[12,13] found a disparity between blood flow to normally perfused and ischemic myocardium after administration

TABLE III

Group IV. Heart Rate and S-T Depression at Rest and During Exercise in Five Control Patients

Case no.	First Exercise Test (control)				Second Exercise Test (control)				Third Exercise Test (control)			
	Heart Rate min^{-1}		Sum of S-T ↓		Heart Rate min^{-1}		Sum of S-T ↓		Heart Rate min^{-1}		Sum of S-T ↓	
	R	Ex	mv	%	R	Ex	mv	%	R	Ex	mv	%
18	69	125	7.5	100	68	131	8.3	111	69	130	5.9	79
19	100	128	13.4	100	94	143	10.2	67	99	144	11.2	84
20	65	109	5.3	100	61	114	5.8	109	73	115	5.9	109
21	65	162	7.7	100	73	162	4.3	56	77	163	4.4	57
22	59	142	7.5	100	62	144	6.9	92	61	140	7.8	104

of dipyridamole, whereas after nifedipine the flow distribution was not different from control values. From the present study it is evident that increased coronary flow is unrelated to the antianginal potency of nifedipine.

Role of coronary spasm: In patients with coronary spasm nifedipine apparently exerts its main effect by a direct influence on the smooth muscle of the coronary arteries. In classic variant angina, this mechanism of action can hardly be doubted,[14] but it is not clear whether it is in effect in stable angina. Because our study did not include patients with variant angina, it is unlikely that the central cardiac effect of nifedipine, which was demonstrated by intracoronary administration of a dose without systemic action, and its antianginal action are due to its action on coronary spasm. An influence on cardiac metabolism may be an important factor. Studies during pacing-induced and exercise-induced angina performed with a different calcium antagonistic drug (perhexiline) showed clear antianginal activity with unaltered hemodynamics; the findings also suggest reduced myocardial oxygen requirements without change in the usual indexes of myocardial energy consumption.[15]

Myocardial function: Inhibition of calcium ion activity in the myocardium leads to a state of contractility with reduced energy consumption. The calcium antagonism does lead to reduced contractility in an isolated heart muscle preparation. However, calcium inhibition can occur in the intact organism without this reduction. Thus, our finding that the indirect indexes of contractility point more toward increased than toward decreased contractility (reduced left ventricular end-diastolic pressure during exercise after nifedipine) does not contradict this hypothesis. No direct measurements of contractility were performed, but in a previous study performed with verapamil,[16] an increased maximal velocity of fiber shortening with decreased left ventricular filling pressure was observed after administration of 10 mg of intravenous verapamil.

Lowering of peripheral resistance: The slightly greater antianginal effect of nifedipine after intravenous than after intracoronary administration could be explained by an additional peripheral action of the intravenous dose, that is, lowering of resistance in the arterial system (afterload reduction); however, it is also possible that 1 hour after the intracoronary infusion there was still remaining activity, which was only potentiated by the intravenous dose.

Conclusion: The mode of action of the calcium antagonist drug nifedipine must include a central cardiac effect. Most likely this is related to an alteration of the calcium-mediated myocardial contraction process leading to reduced oxygen requirements or to increased tolerance of ischemia of the heart.

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PANEL DISCUSSION

Bernard Lown, MD, FACC, Chairman and Moderator

The Future Clinical Role of Nifedipine

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In the examination of a new drug its pharmacokinetic properties must not be ignored. So a few words on that subject are in order about nifedipine. More than 70 percent of the drug is absorbed when taken orally. After ingestion it is detected in the blood within 20 minutes and, when dissolved sublingually, within 10 minutes. Peak blood concentration has been recorded 1 to 2 hours after oral use. The drug is primarily eliminated through the kidney, where 70 to 80 percent is excreted; the biologic half-life of nifedipine is about 4 to 5 hours. Apparently, there is no change in absorption during chronic use, at least in studies of up to 6 months. Nifedipine does not induce liver enzymes in the serum. Unlike the beta adrenergic blocking drugs, nifedipine has no effect on lung compliance or function. No cardiac insufficiency has been observed in patients receiving the drug for as long as 1 year. The drug has no renal or hematopoietic effects, nor has it been shown to modify glucose metabolism in normal subjects or in diabetic patients.

Introduction of a new drug is invariably accompanied by glowing promissory notes and raises expectations seldom fulfilled with further clinical use. Caution and a critical stance should be assumed in considering nifedipine, as is appropriate in the case of all new therapeutic agents. Remarkably, side effects with nifedipine have been relatively few and have been reported in 17 percent of patients studied. In 5 percent of patients toxic reactions were sufficient to discontinue its further use. Generally, the adverse effects have been extensions of the pharmacodynamic properties of nifedipine, such as symptoms of headache and congestion, nausea and vomiting, and dysesthesia and dizziness.

The various reports of this Symposium leave the clinician with some important unanswered questions that relate to the realities of daily practice. First, does nifedipine afford better management for the patient with angina pectoris than is currently provided by nitrates and beta adrenergic blocking drugs? I am not aware that appropriate studies have been conducted that yield adequate information. Until such decisive studies are completed, the evidence at hand does not indicate that the trade-off with nifedipine is advantageous for the patient. The physician in practice need not be the first to abandon the old nor the last to embrace the new.

A second question relates to the weak negative inotropic effects of nifedipine. A recent experience again suggests caution. The antiarrhythmic agent disopyramide phosphate was touted to be free of any significant myocardial depressive effects. Yet now it is clear that it is a powerful negative inotropic drug. Fortunately, nifedipine has a much greater effect on calcium flux in smooth muscle than in cardiac muscle. Nonetheless, rarely is a drug used alone, and in the patient with heart disease, several agents will invariably be administered simultaneously. Drug interactions with nifedipine remain to be defined.

The physician already has a substantial and effective armamentarium for treating the patient with classic angina. However, calcium antagonist coronary vasodilators already have a therapeutic niche for Prinzmetal's variant angina. They may have special application in preventing the deleterious effects of calcium sequestration in mitochondria of injured myocardial cells. But, as with all new drugs, full comprehension of the clinical spectrum of utility of a drug is not provided by the limited experience of the researcher; ultimately, it is the clinician in practice who defines the true value and limitation of a new therapeutic agent.

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Coronary Spasm

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It is a pleasure to comment on the two papers on coronary spasm—the unique and profoundly important studies of Maseri et al.[1] and the studies conducted by Gunther and the group at Harvard[2]—which have further extended the ways in which we can evaluate patients with possible spasm. These studies (and others I will allude to briefly) have, in essence, aroused new interest in the question of coronary spasm as a possible important means of producing some of the clinical expressions of ischemic heart disease. Our understanding of the role of coronary spasm is now in a phase of rapid

evolution. Pathophysiologically, and perhaps therapeutically, this reexamination of coronary spasm may be the most important development that has taken place in many years in understanding the manifestations of ischemic heart disease.

What have we learned to date? One of the lessons that has already become clear is that in the future we had better think twice before dismissing the concepts of such giants as Heberden, Latham and Osler, to name but a few, because the concept of coronary spasm is not new (as so many important notions are not new).

It is also important to place in perspective some of the misconceptions of the first era of coronary arteriography. In that period, the commonly held view was "if you can't see it, it's not there." The symptomatic expression of disease and the clinical diagnosis yielded to the arteriogram as the "definitive" diagnostic modality, the history all too often beginning with the arteriogram. It should be clear by now that, perhaps paradoxically, coronary arteriography set back our understanding of at least some of the clinical expressions of ischemic heart disease, at least where spasm is concerned. We realize this in retrospect, because arteriography was almost uniquely designed to prevent spasm from manifesting itself. Premedication, the routine use of sublingual nitroglycerin before arteriography, the vasodilating properties of contrast material, the concern about performing arteriography during an ischemic episode, and the frequent demonstration that spasm could be provoked by the catheter tip itself (at a time when no symptoms or electrocardiographic changes were observed) all tended to obscure and negate the role of spasm. In retrospect we can see that it seems almost accidental that coronary spasm was arteriographically demonstrated.

The third lesson that one must remember—and this applies to necropsy examination as well—is that disease and its symptoms are frequently dynamic pathophysiologic processes. The anatomic expressions of the disease process itself may be only the tip of the clinical iceberg. At times, pure structure can be indeed misleading, as has been shown in recent years with the advent of "intervention ventriculography" and the diagnosis of aneurysm.

Where do we stand, then, with respect to the role of spasm in the clinical expression of ischemic heart disease? Some answers are in, and others are in the process of evolution. In this discussion, I shall not discuss classic or variant angina pectoris because these will be dealt with in detail in other formal presentations in this Symposium. With respect to resting angina, it is becoming progressively clear that at least some patients, as demonstrated by Maseri, do indeed exhibit spasm—perhaps of lesser degree, perhaps of a smaller vessel, perhaps in zones subserved by collateral vessels—and, therefore, have less ischemia, manifested by S-T depressions rather than S-T elevations. Problems remain in further elucidating this relation. One of them may be the differential therapeutic effect that propranolol may have in patients with variant angina compared with that in patients with the intermediate syndrome.

Vitally important is the possible role of spasm in the etiology of acute myocardial infarction. Maseri has also alluded to this, and it is important to reemphasize that our traditional thinking about acute myocardial infarction has resulted from necropsy data indicating thrombosis or, at times, hemorrhage into the site of plaque disruption as the cause of the acute infarct. However, the thrombosis theory has been controversial for more than a decade. Several studies have shown that thrombosis is frequently absent in patients dying of acute myocardial infarction and, in fact, the older the infarct, the greater the incidence of thrombosis becomes statistically. This has suggested to some that acute myocardial infarction actually causes the thrombosis (and not vice versa). It is possible that a dynamic interplay may take place involving spasm with attendant blood stagnation and platelet clumping, with or without platelet release of vasospastic substances such as thromboxane. A vicious circle may thus be established, resulting in either thrombosis or plaque disruption and hemorrhage. The observations at necropsy may be secondary phenomena.

It is interesting to speculate that Prinzmetal's angina may represent an aborted myocardial infarction, because it is clinically indistinguishable from the earliest stages of an acute infarct. In patients with classic Prinzmetal's angina and documented spasm there is a strong tendency for an acute myocardial infarction to develop subsequently in the myocardial territory of the spastic coronary vessel. In addition, there is a subset of patients with acute myocardial infarction who have angiographically normal or at least nonobstructed coronary vessels. Spasm can frequently be provoked in these patients, who often are heavy cigarette smokers (tobacco being a known vasospastic stimulus). The work of one of our co-panelists, Philip Oliva, also bears importantly on this. Oliva demonstrated beautifully that when intracoronary nitroglycerin is injected in patients with acute myocardial infarction, an increase in vessel luminal size is demonstrable, particularly if the infarct is 6 hours old or less. This observation also suggests that spasm may be playing an important role in the infarction.

Lastly, I would like to address myself to the possible role of spasm in sudden death due to ischemic heart disease. The primary focus has been on arrhythmia itself, this is, the ventricular premature beat as the harbinger of sudden death. However, the underlying arrhythmogenic stimulus has remained totally unclear. It is noteworthy that at necropsy the prevalence of thrombosis is very low in these patients. The syndrome or variant angina may also be a model of aborted sudden death, because during the early period of S-T elevation severe ventricular tachyarrhythmia (or heart block) is frequent. Also, in the study of Weaver et al.[3] in Seattle of patients resuscitated from sudden death, 6 percent of those undergoing subsequent coronary arteriography had insignificant organic obstructions. This strongly

suggests that another mechanism was operative, at least in this subgroup. Certainly, not only could spasm itself be a potent arrhythmogenic stimulus, but also the cessation of spasm could result in the ventricular tachyarrhythmias frequently produced by "reperfusion" experimentally.

Much of this discussion has been hypothetical, and the evidence that spasm is the underlying cause for myocardial infarction or sudden death is still largely anecdotal and indirect. However, there appears to be enough suggestive and rapidly accumulating evidence that spasm plays an important role in the clinical expression of ischemia to warrant making this a major area of future investigation.

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Types of Spasm and Their Diagnosis

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Because this Symposium is directed primarily toward a discussion of spasm, it should be pointed out that there are several types of spasm.

There is catheter-induced spasm, which is a mechanical phenomenon. The spasm is sometimes severe, but no electrocardiographic abnormalities or pain are associated with it. Variant angina has already been reviewed in this Symposium. But there are other types of symptomatic spasm or probable spasm, such as the myocardial infarction that occurs after administration of oxytocic drugs. Fortunately, this is a rare complication because oxytocic drugs are given infrequently (post partum, for example), but it does occur. Older clinicians will remember that at one time Pitressin® was given commonly during gastrointestinal X-ray examination to move the gas shadows away from the region of the gallbladder, and sometimes this would precipitate acute myocardial infarction.

There is myocardial infarction occurring with intracranial hemorrhage; this accounts for the sharp symmetric inversion of T waves in the precordial leads that one sometimes sees with spontaneous subarachnoid hemorrhage. This is a peculiar type of spasm, if it is spasm, because apparently it can be blocked by propranolol, whereas in variant angina propranolol often accentuates rather than relieves the symptoms.

Some patients have myocardial infarction after bypass surgery in the presence of patent grafts. There is a good possibility that spasm is a factor in this condition. Other conditions have been mentioned, including, for example, myocardial infarction without coronary disease. We do not think that this is variant angina in the sense that it has been discussed in this Symposium; Heupler has performed a number of ergonovine tests in these patients, and the results have been uniformly negative. In our institution we have not tried to investigate spasm in patients with severe coronary disease for fear of possible complications.

There are certain situations that are not explained by spasm. I believe that one of these is atypical chest pain. If this remains unexplained after all currently known tests have been performed, then spasm is not a likely explanation for the condition.

The variant form of angina is really a systemic disease. It is not limited to the coronary arteries. Patients with variant angina have a high prevalence rate of Raynaud's phenomenon and migraine, both of which are vascular conditions; occasionally, patients may have abdominal pain, and in one patient we studied this pain was associated with severe spasm of the celiac axis. So far, it has been difficult to track down the exact mechanism of spasm. It has been shown that autotransplantation of the heart does not cure spasm, and this is an effective way to interrupt the coronary nerve supply; I know of four patients in whom this has been tried with uniformly unsuccessful results. Spasm may involve various regions in the coronary arteries, so that it is not always reproducible in identical areas. Sometimes there may be involvement of the right coronary artery, and at other times of the left circumflex or of the left anterior descending coronary artery in the same patient. It is necessary to use multiple leads to be sure about the electrocardiographic abnormalities.

I have been asked how one diagnoses spasm, which is of course, a difficult condition to diagnose. If the pain is of short duration—perhaps a month or so—it is extremely difficult to diagnose spasm clinically and it is impossible to differentiate it from obstructive coronary disease. It is known that patients who have severe obstructive coronary disease may have pain only at rest without any exertional pain; often they have extremely severe obstructions in the coronary arteries, and pain may be recurrent over a considerable period of time without the occurrence of any anginal pain on exertion. In these patients it has been shown in many instances that pulse rate and blood pressure increase during pain

as they do with ordinary classic angina pectoris. The S-T segments may be elevated in these patients. If the history of the symptom is long—a month or more—one may suspect spasm if the patient has pain predominantly at rest. If there is any exertional component, it is minor in the typical case of variant angina pectoris. The pain often wakens the patient at night, although it may occur at rest in the daytime. I do not think one could set the clock by the occurrence of the pain, but repetitive pain at night is characteristic of this condition. Although S-T segment elevation is not invariable in variant angina, its occurrence suggests the diagnosis.

A good thing to do in the hospital, instead of leaving instructions that the patient be given nitroglycerin for pain, is to have the nurse check the pulse rate and blood pressure during pain; if these are both normal, one should suspect that the patient has the variant form of angina pectoris—or no cardiac condition.

In reference to the clinical papers presented, I believe that they reflect what we know of variant angina pectoris and the therapeutic response. We have used nifedipine only in patients who had nonobstructive coronary artery disease or in whom the obstructive component was minor, and we have not had long-term failures such as those described in this Symposium. The patients seemed to continue to do well; the longest duration of therapy has been a little over 3 years in one patient, and he is still doing reasonably well. As Heupler[1] mentioned, alpha and beta blocking agents do not seem to help these patients. Nifedipine is tolerated well, which is fortunate. Nausea is the only side effect we have encountered, and this occurred in only one patient.

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Nifedipine to Preserve Function During Ischemia

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I shall limit my remarks to some of the implications of the data of Clark et al.[1] They opened up a whole new area of interest when they suggested that nifedipine had value in preserving myocardial function when ischemia occurred. The strongest parts of his data are the sequential observations in which the agent was shown to be beneficial in global ischemia; that is, where we can rule out factors relating to coronary blood flow and to hemodynamics, but where we see that this agent primarily had an effect that preserved ischemic myocardial function. The rationale for this effect on ischemic myocardial function relates to a large body of data that suggest that calcium movement into the myocardial cell is an important event in ischemia-induced myocardial injury and also, and perhaps even more important, a critical factor in the effects of transient ischemia on myocardial function.

Lown[2] pointed out in his opening remarks that there are certain unique characteristics of the reperfusion period in terms of the arrhythmias that occur. Certainly, a number of studies suggest that the amount of calcium that enters the myocardial cell in the reperfusion period may be very large and that a major component of injury to the myocardium as a result of transient ischemia—as might occur in the operating room or even during spasm itself—might well be related to this large influx of calcium. Calcium influx during and after ischemia is thought by many to result in mitochondrial damage, contracture and loss of function.

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Nifedipine in Variant Angina and Role of Spasm in Ischemic Heart Disease

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A cascade of information about nifedipine has been presented in this Symposium and I would like to discuss some aspects of the papers that have been presented. First I will consider the effect of nifedipine in patients with Prinzmetal's angina and effort angina, and then

I will discuss the possible role of spasm in the various expressions of ischemic heart disease.

With respect to the use of nifedipine in patients with Prinzmetal's angina, the two conclusions that I drew from the papers by Heupler[1] and Goldberg[2] and their co-workers were: (1) nifedipine is generally effective initially in relieving the ischemic pain of patients with Prinzmetal's angina, and (2) withdrawal of the drug may result in a recrudescence of angina, the recurrent attacks being as bad as or worse than the initial ones. These findings were similar in the two groups, but I also noted some differences. One is that the long-term results were slightly different between the two groups of patients studied. In Heupler's group[1] all the patients had "a good long-term response," whereas in Goldberg's group[2] only five of nine patients maintained a good response. Some others had complications despite either continuation or, in some instances, withdrawal of the drug. So the long-term response may not be the same as the initial response. I also noted some differences in dosages. I believe that Heupler's patients usually received 40 mg/day of nifedipine, with two patients receiving 60 mg, whereas larger doses—60 to 120 mg/day—were used in Goldberg's study. Maybe this accounts, in part, for the differences in long-term results. Also, additional drugs may have been a factor: All of Goldberg's patients continued to receive nitrates while they were taking nifedipine, whereas in Heupler's group of eight patients only three patients took nitrates concomitantly with nifedipine. Therefore, these differences in dosages and in concomitant drug administration might have had an effect on the long-term results.

With respect to effort angina, it is interesting that Moskowitz et al.[3] reported improved exercise tolerance in their patients who received nifedipine despite the fact that the improved exercise tolerance was not associated with a change in the double product (heart rate × systolic blood pressure). This raises the question of what the mechanism is for the improved exercise tolerance. Apparently, nifedipine does increase coronary blood flow, as Kaltenbach[4] pointed out. However, that increase is temporary (it lasted only a few minutes), at least after intravenous nifedipine, and yet the effect on exercise tolerance lasted up to 1 hour after intravenous nifedipine. Lichtlen[5] also demonstrated that regional coronary blood flow is increased, as determined with thallium perfusion scintigraphy and measurement of regional blood flow with the xenon clearance technique. Thus, nifedipine does increase coronary blood flow globally and regionally; but is this the mechanism whereby effort angina is alleviated: I am reminded of a study made a few years ago by Ganz and Marcus,[6] who administered intravenous and intracoronary nitroglycerin to patients with effort angina. They induced angina by atrial pacing and then administered 75 μg of intracoronary nitroglycerin. This substantially increased coronary sinus blood flow, but did not alleviate the angina. Nitroglycerin was then given intravenously, and this produced the expected systemic effect of reducing arterial pressure. As a result of the systemic effect, the angina lessened. So, from the information presented in this Symposium, I am not sure why nifedipine is so effective in effort angina, since (1) this drug had no significant effect on the double product, (2) the increased coronary blood flow did not temporally coincide with the increased exercise capacity, and (3) earlier studies with nitroglycerin indicated that increased coronary blood flow was not the mechanism by which effort angina was alleviated.

Finally, let us consider the role of spasm in the various expressions of ischemic heart disease. At this time (March 1979) there is little question in anyone's mind that spasm is important in patients with Prinzmetal's angina. However, the importance of spasm in the other expressions of ischemic heart disease is less certain. It has been proposed that coronary vasomotion may play a role in patients with effort angina. At this time I am not certain about the role of coronary vasomotion—at the level of either the large epicardial vessels or the small intramyocardial resistance vessels—in effort angina. Interestingly, some of Maseri's patients[7] with resting angina also had effort angina. This observation is not entirely new, because Prinzmetal et al.,[8] in their original paper, pointed out that variant angina often occurs in patients with effort angina at some time in the course of their disease.

In about 40 percent of patients with acute transmural myocardial infarction, we[9] have demonstrated spasm during the first few hours. An interaction among spasm, platelet aggregates and an atherosclerotic plaque may precede occlusive thrombus formation. However, I am uncertain about the relative importance of spasm in the pathophysiology of acute myocardial infarction. In their recent studies, Maseri et al.[10] imply that spasm is an important factor because several patients with previously detected spasm subsequently had occlusion of the artery at the site of the spasm and an infarction in the distribution of the occluded artery. However, each of their eight patients had resting angina with S-T segment elevation—a group of patients we might expect to have spasm—before transmural infarction occurred. A distinction must be made between patients with acute infarction and preceding pain at rest with S-T elevation and patients without preceding electrocardiographic changes or symptoms because the relative importance and incidence of spasm may be different.

In conclusion, I think we would agree that spasm plays an important role in Prinzmetal's angina and that nifedipine is often successful therapy. The role of spasm in other expressions of ischemic heart disease is less clear. Spasm and atherosclerosis may work in concert; if so, it will be important to ascertain their specific interrelation in the various manifestations of ischemic heart disease.

From the University of Colorado Medical Center, Denver, Colorado.

Address for reprints: Philip B. Oliva, MD, Chief, Division of Cardiology, Denver General Hospital, Eighth and Cherokee Streets, Denver, Colorado 80204.

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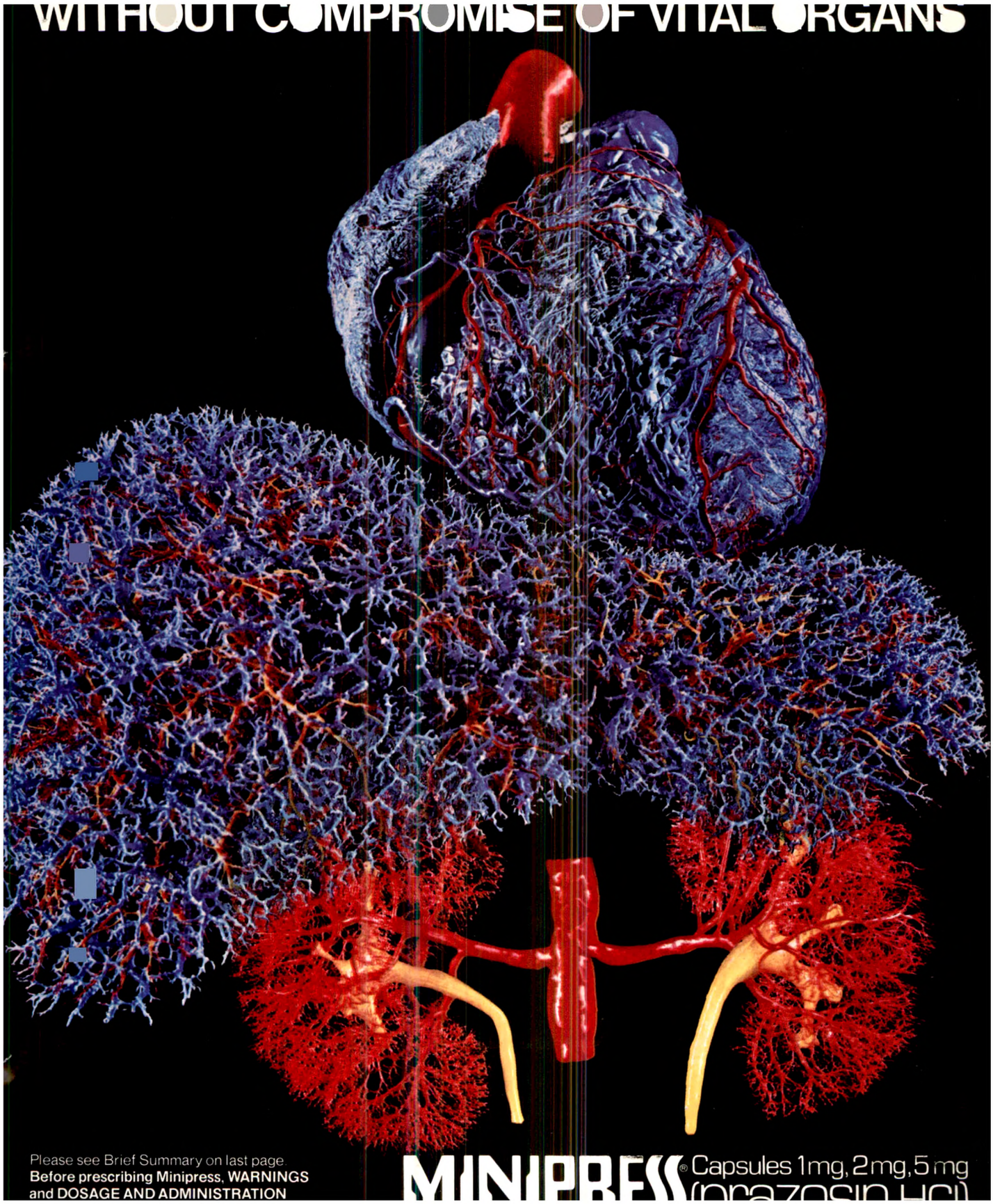
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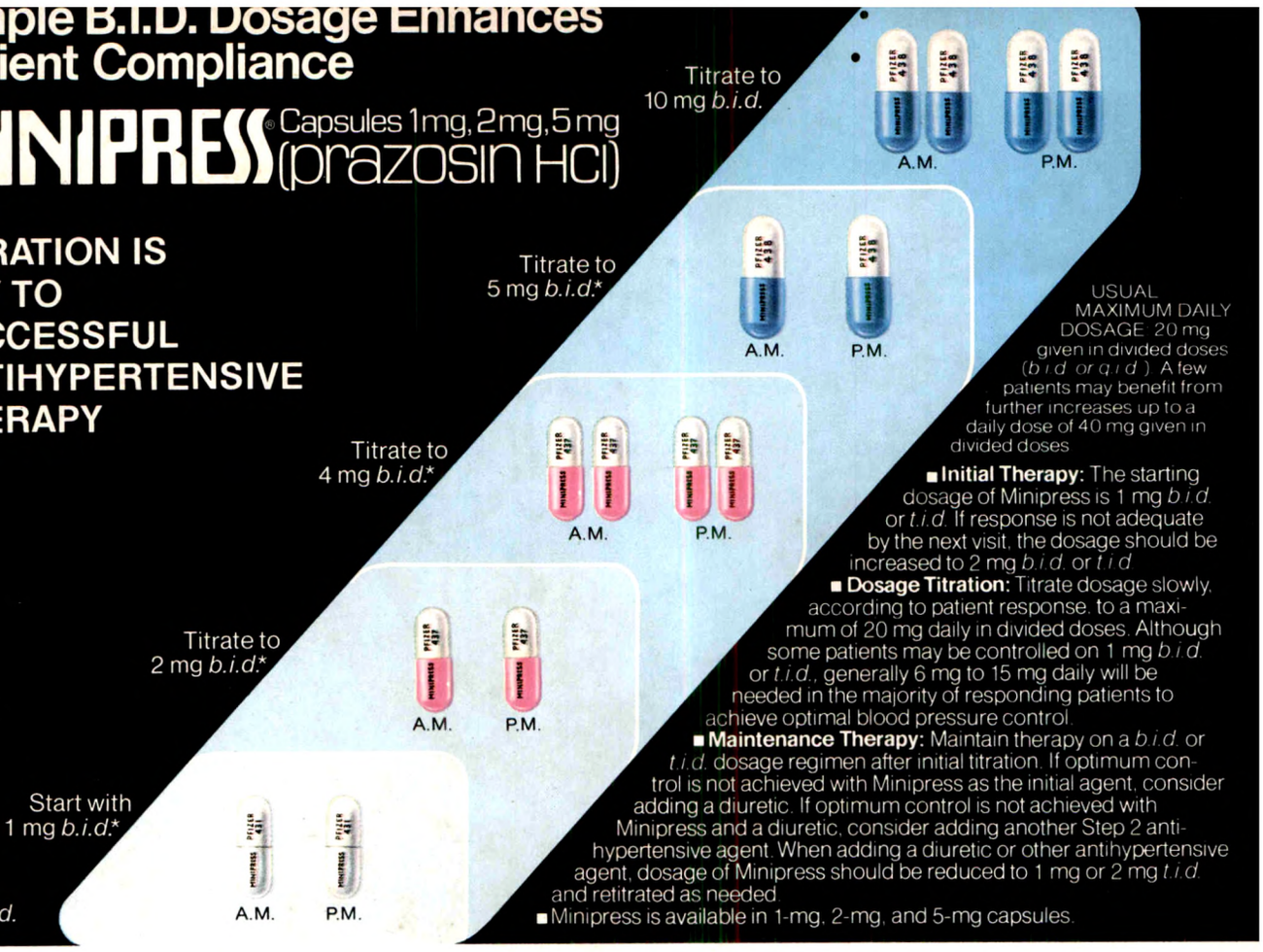

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If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS: The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established).

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, incontinence, impotence.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION: The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg two or three times a day. (See Warnings).

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

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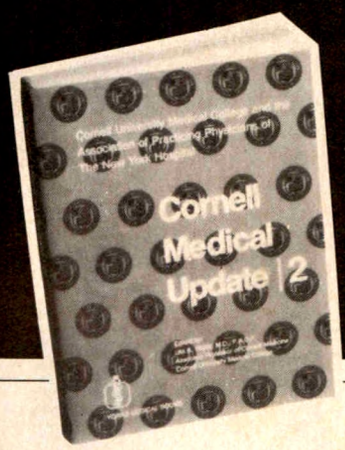

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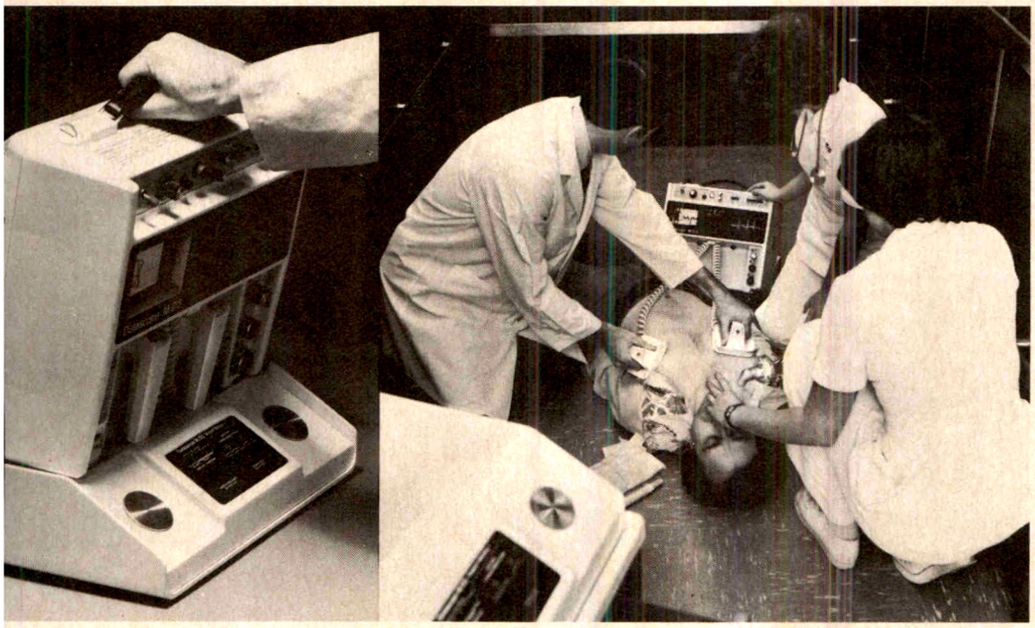

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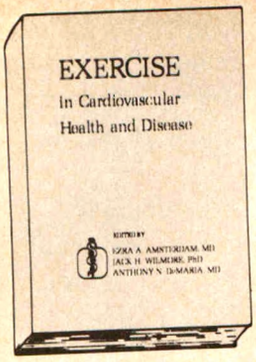

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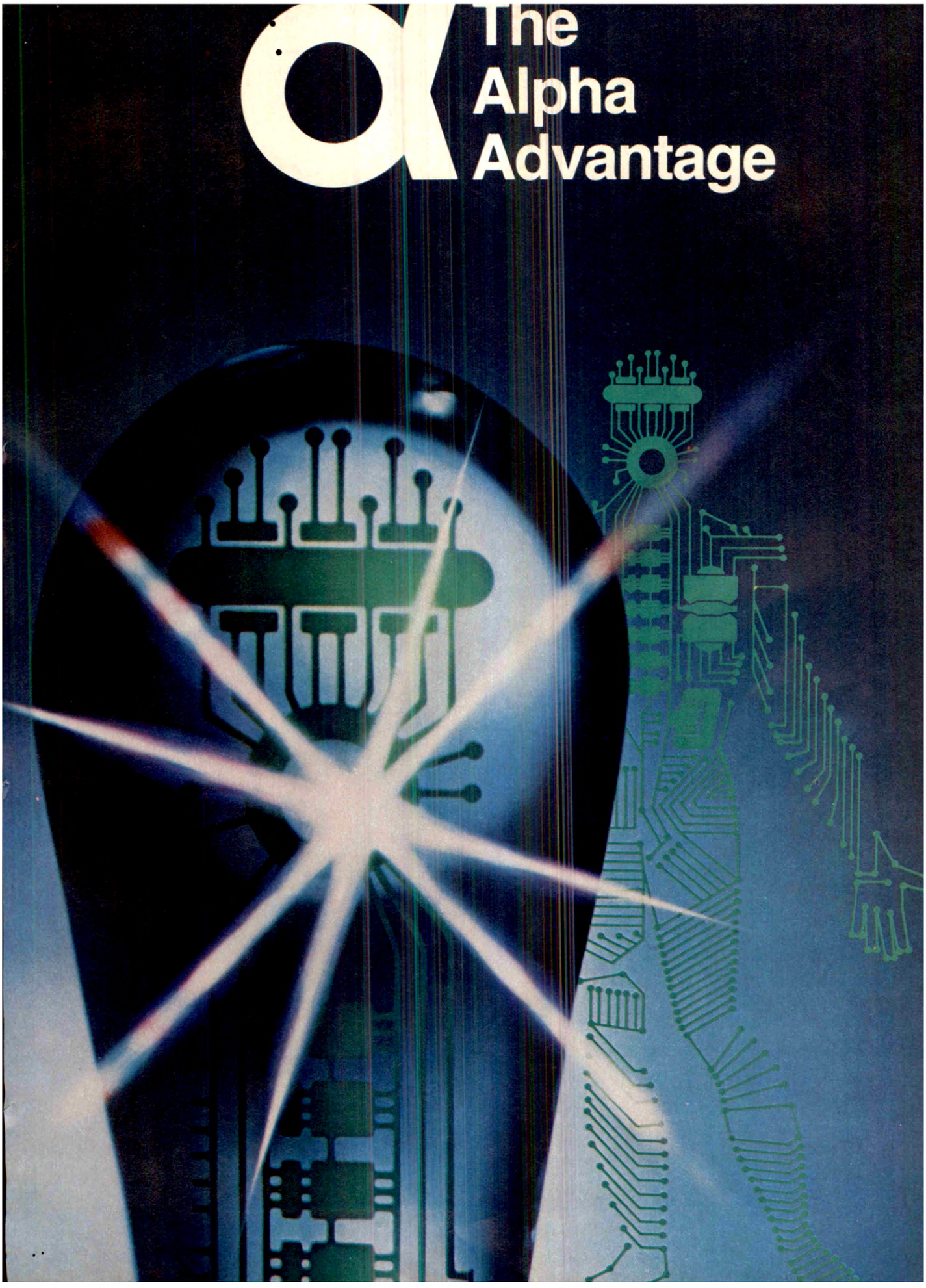

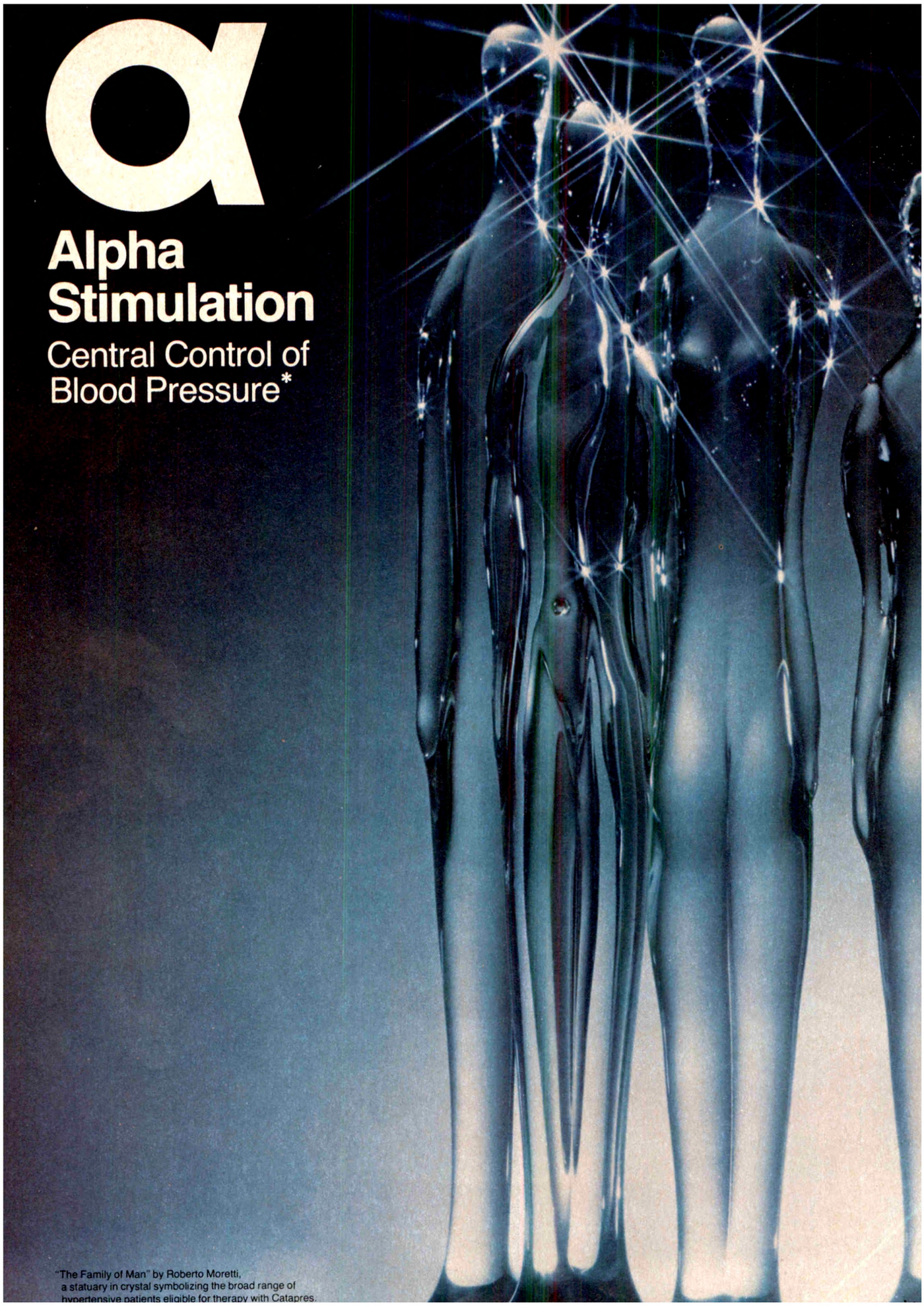
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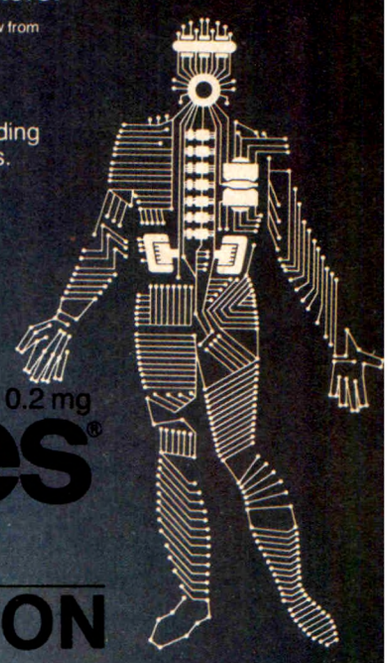

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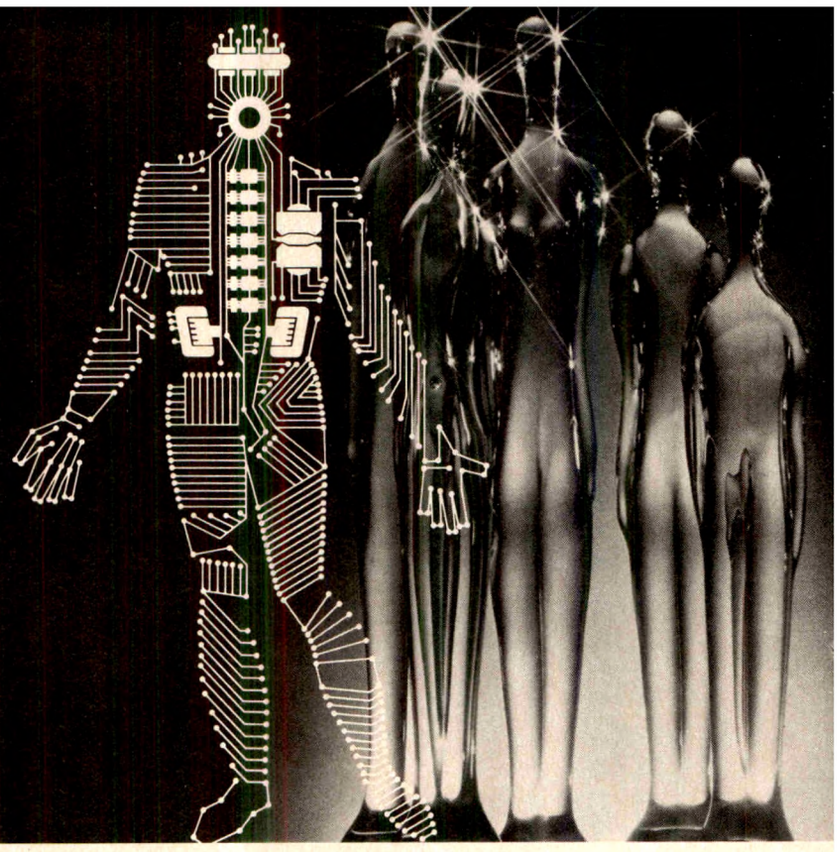

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(clonidine hydrochloride)
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Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness ar sedation. Constipation, dizziness, headache, and fatigue have been reporte Generally these effects tend to diminish with continued therapy. The followir reactions have been associated with the drug, some of them rarely. (In sor instances an exact causal relationship has not been established.) These includ Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities liver function tests; one report of possible drug-induced hepatitis without icter and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlo thalidone and papaverine hydrochloride. Weight gain, transient elevation of bloc glucose, or serum creatine phosphokinase: congestive heart failure, Raynauc phenomenon; vivid dreams or nightmares, insomnia, other behavioral change nervousness, restlessness, anxiety and mental depression. Also rash, a gioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associate with a rash, impotence, urinary retention, increased sensitivity to alcohol, drynes itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomasti weakly positive Coombs' test, asymptomatic electrocardiographic abnormaliti manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or a sent reflexes and vomiting followed the accidental ingestion of Catapres (clonidi hydrochloride) by several children from 19 months to 5 years of age. Gast lavage and administration of an analeptic and vasopressor led to complete r covery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minu intervals usually abolishes all effects of Catapres, (clonidine hydrochloride) ov dosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 m (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 100

For complete details, please see full prescribing information.
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Introduction: Recent Perspectives on Hypertension and The Heart

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The first descriptions of hypertension stemmed from pathologic studies of cardiac hypertrophy in renal disease. Despite these letters of credence and the intuitive analyses of Bright and Mahomed[1] and despite the importance of hypertension as a cause of cardiac disease,[2] there has been a long period of estrangement from hypertension by cardiologists in both research and practice. The causes of that apparent lack of interest were many. On a superficial level, but one with marked practical impact, were the pressures of bedside teaching. Hypertension as a source of exciting clinical signs is a pale competitor for valvular or congenital heart disease; measuring blood pressure is obviously not as stimulating as deciphering an arrhythmia. More important, there was little sense of urgency in a mostly asymptomatic disease at a time when medical practice was more attuned to crisis management than to long-term prevention and to treatment of apparently well adults.

Of particular significance, also, was the little stimulus to cardiac studies from high blood pressure research. Because cardiac output was thought to be normal in most cases, the essential fault in hypertension was related to alterations in peripheral resistance, and studies of the heart were not thought likely to contribute much of fundamental significance. High blood pressure research focused on factors that influenced vessels or overfilled them; as such, it appeared to be divorced from the preoccupations of cardiologists and from the intense efforts that went into the studies of cardiac performance and hypertrophy.

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Cardiogenic Hypertension

Role of increased cardiac output: Interest was revived in a possible "role of the heart in hypertension"[3] when investigations in the past decade described a high cardiac output in patients with labile hypertension,[4] renal arterial disease[5] and primary aldosteronism[6] as well as in a subtype of severe essential hypertension.[7] Various types of experimental hypertension also appeared to be initiated by an increase in cardiac output.[3,8] However, these reports were mostly based on determinations of cardiac output and therefore left unresolved the problem of active cardiac participation in hypertension. The description of a high output in a hypertensive state does not define the role of increased flow in the production of high arterial pressure nor does it allow the conclusion that this hypertension is cardiogenic.[9] That term was introduced by Freis[10] to describe hypertension due to primary increases in cardiac action. However, in many patients with high output hypertension, the heart is merely responding to increased blood volume or to venoconstriction and central relocation of blood.[11] More important, it was repeatedly shown that prevention of the increase in output in experimental conditions did not prevent the development of hypertension.[8]

The controversies surrounding the importance of cardiac output in the initiation of hypertension have been animated and fruitful. They have often focused on the problem of autoregulation and dealt little, if at all, with a specific cardiac role in the disease. In the traditional models of Borst[12a] and of Guyton,[12b] hypervolemia and increased cardiac output were projected as key factors in the initiation of hypertension. However, an emerging trend appears to favor a primary role for increased vascular resistance even in volume-dependent hypertension.[13] However, these discussions, although very important in the understanding of circulatory control, are really not germane to the definition of car-

diogenic hypertension. An increased output is indeed found in many instances of spontaneous or experimental hypertension,[3,8,11] but, contrary to past opinions,[3] the role of the heart in hypertension cannot be defined in terms of cardiac output alone.

This does not mean that a primary increase in cardiac performance cannot participate in the development of some types of hypertension[11,14] or affect their clinical evolution.[15] Studies with long-term stellate stimulation or prolonged intracoronary dobutamine infusion have shown that hypertension can be initiated by a primary increase in cardiac inotropism. The initial increase in cardiac output produced by those stimuli was not related to fluid overload. However, the role of the heart in these types of hypertension was defined not by this initial rise in output but rather by the fact that the stimulus was primarily directed to the heart.

Cardiovascular Reflexes

All of the foregoing considerations have dealt with cardiac pumping as a determinant of arterial pressure, but the heart may well have another role in hypertension. Emerging evidence indicates that it can be a source of potent pressor reflexes.[16,17] In retrospect, it does not appear likely that physiologic monitoring of arterial pressure would be limited to only one or two vascular areas. The large differentials in pressure across the heart and great vessels as well as cardiac sensitivity to alterations in venous return or in resistance to ejection suggest that important information could be generated from these areas to help control the circulation. Chemoreflexes from the heart have been described by Comroe[17] and James et al.[18] among others; they can be stimulated by anoxia or by specific receptors to veratrum or serotonin. If the blood can be likened to a computer tape, the heart and lung vessels would be important strategic sites to decode messages.

To date, cardiac reflexes have been related clinically only to some types of paroxysmal hypertension,[17,19,20] particularly those that are associated with coronary insufficiency or that follow bypass surgery. Whether they have an ongoing function in chronic hypertension remains to be determined. It is conceivable that some hyperkinetic states alter arterial pressure as much by altered neural input from a disordered cardiac action as by their increased rate of blood flow. Along the same speculative lines, it has been suggested that the antihypertensive effect of beta adrenergic blockade could be related in part to a reflex toning down of sympathetic activity secondary to less forceful distortion of some cardiovascular receptors.

Cardiac Hypertrophy in Hypertension

A rapidly developing area is the study of the cardiac hypertrophy of hypertension and its reversal by some antihypertensive measures. A simple mechanistic view of the relation between increased pressure load and ventricular hypertrophy is, in my opinion, no longer tenable.[21] Many factors can modulate the hypertrophic response to a rising arterial pressure or to maintained hypertension. Of those discussed elsewhere in this Symposium,[22] the rate of pressure rise, the influences of associated diseases and the subtle effects of malnutrition or alcoholism are of particular importance clinically. Still to be fully elucidated are the reasons for the frequency of cardiomegaly among hypertensive patients from Africa[23] or from lower socioeconomic classes.[24]

The practical implications of these observations are obvious; they include not only a better understanding of cardiovascular hypertrophic responses but also the possibility of reversing structural lesions by antihypertensive therapy.[21] Results from different centers[25–27] suggest a significant difference among various antihypertensive drugs as regards their potential for reversing cardiac and vascular hypertrophy. Reversal of hypertrophy appears linked to blood pressure control by drugs that reduce or at least do not stimulate adrenergic activity.[21] This can be seen in the results of Sen et al.[25] in cardiac hypertrophy of spontaneously hypertensive rats, in those of Yamori[26] in cerebral and mesenteric arteries of the same model and in those of Foidart et al.[27] in vessels of renovascular hypertensive rats.

Results obtained in experimental models of hypertension: These have added an important practical aspect to the long-standing controversy regarding the efficiency of a hypertrophied heart. Reversal of hypertrophy by blood pressure control is demonstrably possible, but if hypertrophy is not really deleterious, why attempt to reverse it? If its reversal is indicated, what would be the influence on cardiac performance of a process that leads to a smaller muscle mass with increased collagen concentrations?[25] Some answers to these questions are beginning to be outlined, but much more is needed for definitive solutions. Of particular importance is the need to differentiate carefully between the intertwining effects of a decrease in blood pressure, a reduction of myocardial mass, a relative increase in collagen and possible associated myocardial disease.[28,29]

Biochemical studies of myocardial changes in hypertension: Such studies have opened new avenues for therapeutic intervention. The evolution of cardiac hypertrophy with aging in spontaneously hypertensive rats was found to be associated with different rates of myosin and collagen synthesis.[30] Attempts to reduce collagen synthesis by different drugs, such as colchicine, penicillamine and beta aminoproprionitrile, have been successful both in the heart[31] and in vessels[32,33] of different experimental models of increased afterload. Long-term treatment with reserpine also reduced collagen content of mesenteric vessels in renal hypertensive rats.[27] Although the myocardial concentration of collagen did not appear to influence significantly cardiac function curves[28] or velocity of papillary muscle contraction,[31] it would probably interfere with myocardial compliance. More important, perhaps, collagen content of vessel walls is said to play an important role in vascular complications of hypertension.[32] Thus, new fields for therapeutic intervention in hypertension and in myocardial disease could conceivably be opened up if future studies would substitute present speculations and if ways could be developed to influence selectively

the synthesis of different types of cardiovascular proteins.

Hemodynamic factors: To the extent that hypertension is a hemodynamic abnormality, careful study of cardiac factors might lead to better understanding of the heart's participation in circulatory control and of its reaction to abnormal loads. Cross-fertilization among different disciplines is already bearing significant fruits for both patients with hypertension and those with cardiac disease. Thus, until recently, little was known of coronary blood flow in hypertension. Marcus et al.[34] have pioneered in this field by demonstrating a reduced coronary reserve in hypertensive models. As renewed interest stimulates research, questions multiply, an obvious one among others being the effect of hypertension on coronary dynamics and collateralization after an infarct.

Humoral factors: In another area, the close interrelation between humoral factors and hemodynamic effects that characterize hypertension research has already been in increased understanding of some aspects of cardiac decompensation.[35,36] Secondary aldosteronism was shown to play an important role in heart failure,[35] and studies of plasma renin activity revealed a wide pattern of abnormalities in patients with failure.[36] Stimulation of the renin-angiotensin-aldosterone system by cardiac decompensation could play an important role in both its hemodynamic and volume abnormalities. Davis[35] has stressed the importance of elevated aldosterone levels for the salt and water retention of heart failure and for resistance to diuretic therapy. Angiotensin II could be a factor in the elevated peripheral resistance seen in many forms of low output cardiac failure.[37] Thus, interference with the renin cascade by converting enzyme inhibition seemed a logical approach to the treatment of resistant heart failure[37,38]; it could help alleviate both its metabolic and its hemodynamic derangements. Captopril has been shown in hypertensive patients to lower peripheral resistance without increasing preload[39] and to help control secondary aldosteronism.[40] Early results in resistant heart failure in normotensive patients seem promising, but the true potential of that new approach remains to be evaluated.

In this Symposium, reviews of recent advances have helped answer some questions and have uncovered many more. The role of the heart in hypertension has emerged as much more important and complex than previously thought. Better care for patients will evolve from this continued dynamic interaction between fundamental and clinical research. Hypertension has proved to be one of the more frequent and important causes of cardiac disability; a thoughtful approach to its problems will be more fruitful in the long run than cook-book recipes. Cardiologists have an important contribution to make in this respect.

Acknowledgment

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Coronary Pressor Reflexes

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The heart differs from other cardiovascular reflexogenic structures because it has two prominent inputs to the central nervous system. One input is spinal and is mediated by afferent cardiac sympathetic nerve fibers. The other is medullary and is mediated by afferent vagal fibers. The number of fibers projecting centrally appears to be similar in the two systems. The reflex effects produced by excitation of the two inputs are complicated and can be either pressor or depressor. However, reflex pressor effects seem to be more prominent for the spinal input and reflex depressor effects more prominent for the medullary input.

As might be anticipated from its central position in cardiovascular function, the heart is a rich source of afferent nerve fibers projecting to the central nervous system. Furthermore, the heart differs from the sinoaortic regions in having two prominent inputs to the central nervous system. A simplified scheme of these inputs and their synaptic connections is shown in Figure 1. One input pathway is by way of the vagus and has its cell bodies in the nodose ganglion. The first central synapses of this pathway are probably in supraspinal structures such as the medulla. The other input pathway is by way of afferent fibers traveling with the cardiac sympathetic nerves, the afferent sympathetics. The nerve cell bodies are located in the dorsal root ganglia of the upper five thoracic segments of the spinal cord and their first central synapses are probably in the spinal cord.

For reasons that are historic and experimental, the vagal input has received the greatest attention. However, it is important that there seems to be no numeric difference between the vagal and spinal inputs with respect to afferent fibers relaying information to the central nervous system. Thus, there are about 300 myelinated and about 1,900 unmyelinated afferent cardiac vagal fibers coming from one side of a cat's heart[1] and there are about 300 myelinated afferent cardiac sympathetic fibers in the left inferior cardiac nerve of the cat.[2] The number of unmyelinated fibers in the afferent sympathetic input pathway is unknown because the signal to noise ratio is likely to be very low, there being 20,000 to 30,000 unmyelinated efferent axons in the inferior cardiac nerve.

Reflex Effects Mediated by Vagal and Sympathetic Afferent Cardiac Fibers

Not only are there two prominent input pathways from the heart to the central nervous system, but also each of these pathways has diverse reflex or output effects. This may not be surprising given the variety of functionally and anatomically distinct structures that constitute the heart, namely, two atria, two venticles, the three layers of each chamber, the valves in each chamber and the coronary blood vessels. Added to this is the fact that each of these structures contains receptors that have projections passing centrally along the two different input pathways. Excitation of various groups of vagal afferents may produce one or another of the following reflex effects: tachycardia with relatively little change in blood pressure[3]; bradycardia and hypotension[4]; and tachycardia and hypertension.[5] Excitation of afferent cardiac sympathetic

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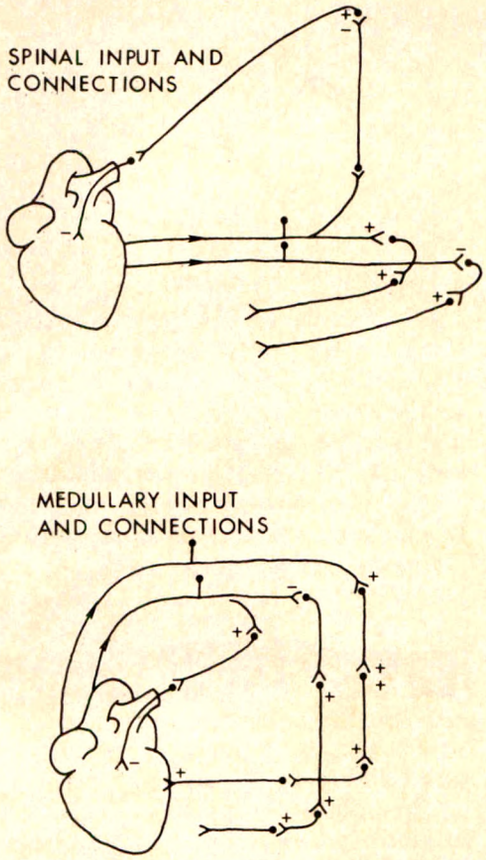

FIGURE 1. Diagram of spinal and medullary inputs from the heart. + = excitation; − = inhibition. Input direction indicated by **arrowheads** on afferent projections. Spinal input projections are excitatory and inhibitory on sympathetic outflow and inhibitory on vagal outflow from the medulla. Medullary input projections are mainly inhibitory to the sympathetic outflow but can be excitatory; they are excitatory to the vagal outflow.

nerve fibers may produce inhibition[6] or excitation[7] of efferent sympathetic discharge and hypertension[8] or hypotension.[9] On the basis of currently available evidence it appears that the reflex effects of excitation of the vagal input are mainly inhibitory whereas the reflex effects of afferent sympathetic excitation are mainly excitatory. However, this assessment may have to be revised as further experimental data become available.

Cardiac receptors can be separated on an anatomic basis into different categories. The receptors are located in each of the cardiac chambers, in the endocardium, epicardium and myocardium and in or near the coronary vessels. Thus, we have atrial, ventricular and coronary receptors as well as endocardial, myocardial and epicardial receptors. Because receptors with afferent vagal fibers will be discussed subsequently in this Symposium, I will emphasize the afferent sympathetic projections from cardiac receptors.

The afferent cardiac sympathetics: Several pathophysiologic studies indicated that afferent cardiac sympathetics were an important pathway mediating pain of cardiac origin.[10–12] The significant evidence was that angina in man and the pseudaffective reaction in animals produced by coronary occlusion were abolished by sectioning these nerves. Pseudaffective reaction is a term introduced by Sherrington[13] to describe reaction in an animal whose objective manifestations indicate a painlike response. Activity from these afferents was directly recorded during myocardial ischemia (Fig. 2), but the exact mechanism by which this stimulus produced excitation was not determined.

Cardiac receptors: After that study it was shown[7] that increases as well as reductions in coronary flow could excite afferent cardiac sympathetic fibers. Since then other investigators have also shown that a number of stimuli such as changes in hydrogen or potassium concentrations can excite afferent cardiac sympathetic fibers.[14] However, most of the receptors studied by Brown and Malliani[7] (1971) were not tonically active, although an earlier study[9] had indicated that tonic activity linked to the pressure pulse was likely to be present in some fibers. This point was established definitely by Malliani et al.[15] and has been confirmed by others.[16] The tonically active receptors are present in all cardiac chambers and, although not always strongly correlated with normal hemodynamic events, they clearly signal abnormal pressures. An interesting recent finding is that these receptors as well as some with vagal axons may sometimes have receptive fields of several square centimeters.[17]

What are the cardiovascular reflex effects produced by excitation of these receptors? Initially it was shown that either excitation or inhibition could be produced when efferent sympathetic discharge was used as an indicator of reflex effects.[21] Subsequently, experiments in which blood pressure, heart rate and myocardial contractility were measured[8,18,19] showed increases in

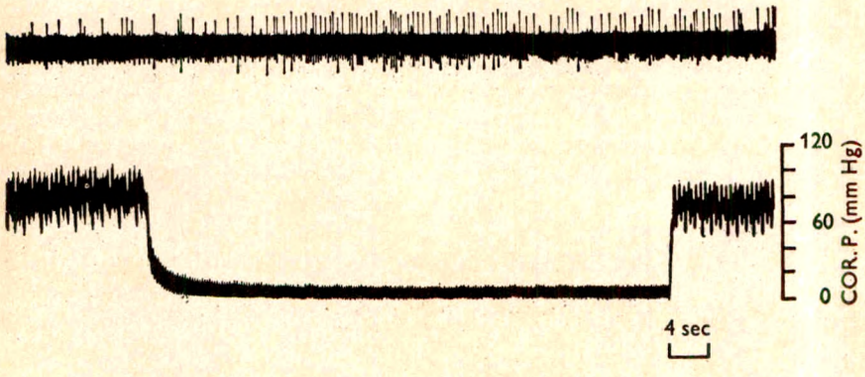

FIGURE 2. Effect of myocardial ischemia on an afferent unit in the inferior cardiac nerve (**top tracing**). The sudden decrease in coronary pressure (COR. P.) (**bottom tracing**) occurred when the coronary inflow was stopped. There was some background activity and this showed a marked increase during ischemia. (Reproduced by permission from Brown and Malliani.[7])

all of these variables that were abolished by alpha or beta blocking agents, or both (Fig. 3).[8] Direct recordings from cardiac and other efferent sympathetic fibers confirmed the excitatory nature of these reflexes. Moreover, cardiac vagal efferent discharge was inhibited, indicating a medullary projection from the spinal input.[20] However, it has recently been shown that low frequency stimulation of afferent cardiac sympathetic fibers may cause depressor effects.[21,22]

Pathophysiologic Implications

Given the complex reflex effects produced by the spinal input from the heart and an even more complicated situation with respect to the medullary input from the heart, it is likely that a large variety of reflex responses will be produced from the heart in intact animals under physiologic and pathophysiologic circumstances. For example, many animals have a marked increase in sympathetic discharge during coronary occlusion after vagotomy; some of this is probably mediated by afferent cardiac sympathetic fibers since arterial blood pressure may not change.[23] Furthermore, the increase can occur after sinoaortic denervation as well. However, coronary occlusion after sinoaortic denervation but with intact vagi can produce bradycardia and hypotension.[23] In both types of experiment the responses are not uniform from animal to animal although one type of effect predominates in a given animal; this variability complicates matters even further. It is likely that the apparent complexity of cardiac reflexes is due to our lack of understanding of some basic mechanisms involved in their genesis.

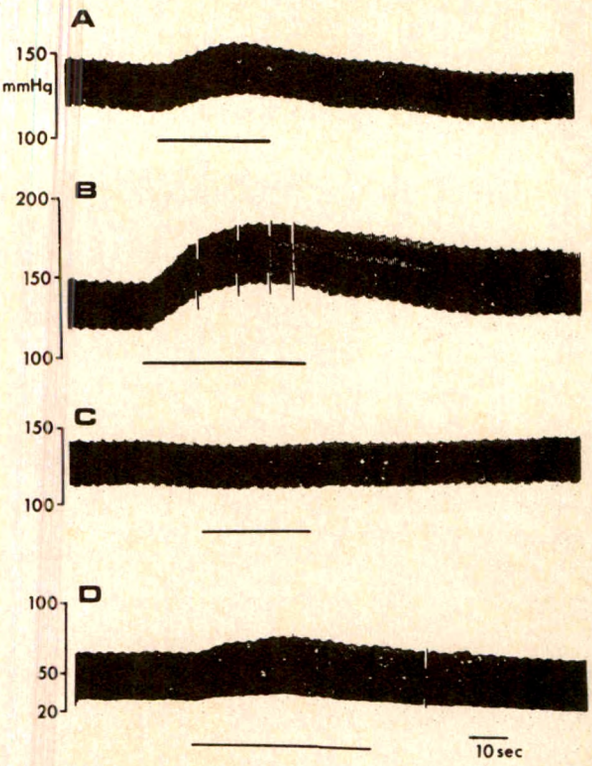

FIGURE 3. Blood pressure response to stimulation of the central end of the cut inferior cardiac nerve. **A,** response with all other nerves intact. **B,** response after bilateral cervical vagotomy. **C,** response after section of all central sympathetic connections from the stellate ganglion. **D,** response after bilateral cervical vagotomy in a spinal animal. (Reproduced by permission of the American Heart Association, Inc., from Peterson and Brown.[8])

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Anatomic and Physiologic Considerations of a Cardiogenic Hypertensive Chemoreflex

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Within both human and canine hearts there is a mass of chemoreceptor tissue lying just between the origins of the aorta and pulmonary artery and receiving its blood supply from the proximal portion of the left coronary artery. In the dog this is considered to be the site of origin for a powerful hypertensive reflex stimulated by serotonin. There is brief generalized arterial vasoconstriction, except for the coronary and pulmonary arteries. The afferent limb of this cardiogenic hypertensive chemoreflex courses in thoracic branches of the vagus. Autonomic efferent responses are both vagal and sympathetic events. These include simultaneous positive and negative inotropic effects on the atria, a positive inotropic effect on both ventricles, positive and negative chronotropic actions and similarly mixed dromotropic effects. Methods for separately identifying and quantifying these responses are discussed and illustrated. Vagotomy eliminates the reflex, as does the administration of cyproheptadine (but not methysergide). Among possible human counterparts for this cardiogenic hypertensive chemoreflex are the pressor responses associated with angina pectoris, with very early acute myocardial infarction and after certain forms of cardiac surgery such as saphenous vein bypass grafting.

In seeking to understand the cause of hypertensive diseases, most investigors have directed their attention to the pathophysiologic basis for increased arterial resistance, although there is growing appreciation that the behavior of the heart itself may be an important fundamental contribution to the development of sustained hypertension.[1] In this report we present anatomic and physiologic aspects of a cardiogenic hypertensive chemoreflex, the manifestations of which include sudden vasoconstriction coupled with simultaneous increase in contractile strength of the heart.[2,3]

Historical Aspects

For most cardiovascular physiologists the word chemoreflex elicits an immediate image of the carotid body, even though chemoreceptor tissue has long been known also to exist within and near the heart.[4,5] For many years the only familiar cardiogenic chemoreflex has been the Bezold-Jarisch response, characterized by bradycardia and hypotension and usually produced experimentally by the epicardial application of veratridine or nicotine. Although some have considered this depressor reflex to be no more than a laboratory curiosity, certain clinical manifestations of acute posterior myocardial infarction closely resemble the Bezold-Jarisch response.[6] One possible mediator for eliciting this depressor reflex is serotonin, which can cause hypotension and bradycardia when administered into appropriate portions of the coronary circulation of the dog.[2,7]

In 1939 Comroe[8] described a hypertensive chemoreflex that he said originated within "aortic bodies." However, his own anatomic studies

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described a blood supply to these structures that came from the coronary circulation. Eckstein et al.[9] later reported a hypertensive response that could be elicited from certain chemoreceptors, the blood supply of which nearly always came from the proximal left coronary artery of the dog; furthermore, they demonstrated that the hypertensive response could be produced with serotonin (5-hydroxytryptamine), a naturally occurring substance carried in virtually all mammalian circulations bound to platelets.

For several years my colleagues and I have investigated this cardiogenic hypertensive chemoreflex in the experimental laboratory[2,3,10–12] and have studied its possible counterpart in human beings.[13] One of its distinguishing features is the magnitude of hypertension produced, aortic pressure almost doubling within a very few seconds (Fig. 1). Both it and the Bezold-Jensen response can be elicited by serotinin,[2,7] but their physiologic features are virtually mirror images.

Anatomic Basis of the Cardiogenic Hypertensive Chemoreflex

Location and blood supply of chemoreceptor tissue: This tissue is found near the origin of the aorta and pulmonary artery[4,5] and has been shown in several species to receive its blood supply from the proximal coronary circulation.[2,8,9,14] Although it has been suggested that these are aortic bodies,[8,9] it seems to us more appropriate to consider them a portion of the heart since they receive their blood supply from the coronary arteries. The chemoreceptor artery nearly always originates from either the main left coronary artery or from the first few millimeters of the left anterior descending artery or its left circumflex division.

Histology: In histologic appearance these coronary chemoreceptors resemble the carotid body (Fig. 2 and 3). They are organized in grape-like clusters around a small artery either at its terminus or around one of its branches, there most often being several such chemoreceptors. Nerves and ganglia abound in this region of the heart, and one or more of the tiny chemoreceptors (less than 1 mm in maximal dimension) are sometimes incorporated within or attached to such neural structures. Both the histologic appearance and the coronary blood supply of these chemoreceptors are similar in human and canine hearts.[2,14]

Physiologic confirmation: Four different physiologic experiments[2] indicate that these particular chemoreceptors are responsible for the cardiogenic hypertensive chemoreflex. (1) Careful cannulation of tiny proximal branches of the left coronary artery of the dog and selective injection of serotonin there will produce the reflex. (2) Injection of serotonin beneath epicardial fat directly over the main left coronary artery will produce the reflex. (3) Local anesthesia of this same region by the infiltration of lidocaine will abolish the reflex. (4) Afferent neurograms recorded from the vicinity of the coronary chemoreceptor show appropriate activity just before the onset of the hemodynamic response and appropriate silence when the chemoreflex is abolished with cyproheptadine, and afferent neural traffic recovers concomitantly with recovery of the reflex when the effect of cyproheptadine wears off.[10] Injection of serotonin into the root of the aorta, the descending aorta, the right atrium or the pulmonary artery does not elicit the cardiogenic hypertensive chemoreflex, and the selective arterial administration of serotonin in the vicinity of the carotid bodies fails to produce the response.

Reflex pathways: Once the reflex is elicited, afferent impulses course by way of the thoracic branches of the vagus nerves, particularly the left and right recurrent cardiac nerves.[10] This afferent route serves to differentiate the cardiogenic hypertensive chemoreflex from a different cardiogenic reflex described by Brown and Malliani,[15] which has its afferent pathway through spinal sympathetic nerves. Another distinguishing feature is the weaker pressor response of the Brown-Malliani reflex. Efferent neural pathways for the cardiogenic hypertensive chemoreflex are both vagal and sympathetic, and there appears to be no preferential route except as may be deduced from the changes in cardiac contractility[3] and from the nature of responses within certain vascular beds.[12] Those responses will be discussed later.

Anatomically, the cardiogenic hypertensive chemoreflex may thus be considered to originate within che-

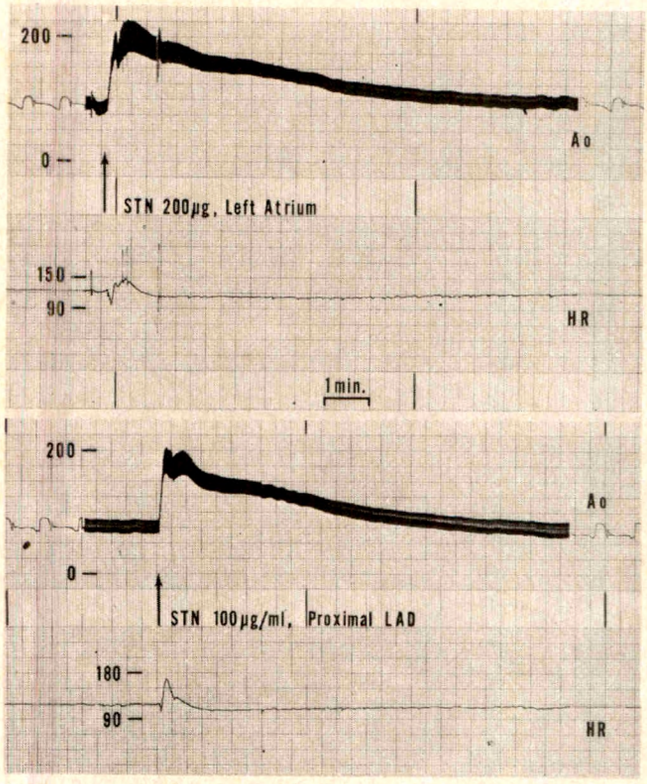

FIGURE 1. Injection of serotonin (STN) into either the left atrium as a bolus or directly into a branch of the proximal left coronary artery (LAD) of an anesthetized dog produces similar abrupt hypertension. Ao = aortic pressure (mm Hg); HR = heart rate (beats/min). (Reprinted from James et al.[2] by permission of the American Heart Association, Inc.)

moreceptor tissue lying between the aorta and pulmonary artery and to receive its blood supply from the proximal left coronary circulation. This tissue and its nutrient coronary branch are similar in human and canine hearts. The afferent pathway of the reflex is through the vagus nerve and its efferent paths include both vagal and sympathetic branches.

Physiologic Components of the Cardiogenic Hypertensive Chemoreflex

Time course: Within about 5 seconds after the administration of serotonin, central aortic pressure virtually doubles (Fig. 1). This abrupt and profound hypertension is the consequence of simultaneous peripheral vasoconstriction and a positive inotropic response by both ventricles (Fig. 4). Both the reflex vasoconstriction and the accompanying (and preceding) afferent neural traffic are rather brief, lasting only a matter of a few seconds, but the resulting aortic hypertension is of longer duration. There is a more modest hypertension of gradual onset that occurs if serotonin reaches the adrenal glands, and it can be eliminated by prior occlusion of adrenal arteries and veins.[3] Depending on the manner of administering serotonin, this latter type of hypertension extends the duration of the reflex response for up to 10 minutes, but only the initial minute or so is due to the chemoreflex.

Flow patterns: Preliminary studies of flow patterns within selected vascular beds have demonstrated that the coronary and pulmonary arteries do not participate in the reflex vasoconstriction.[3,13] Maximal constriction occurs in the mesenteric and renal circulation, whereas

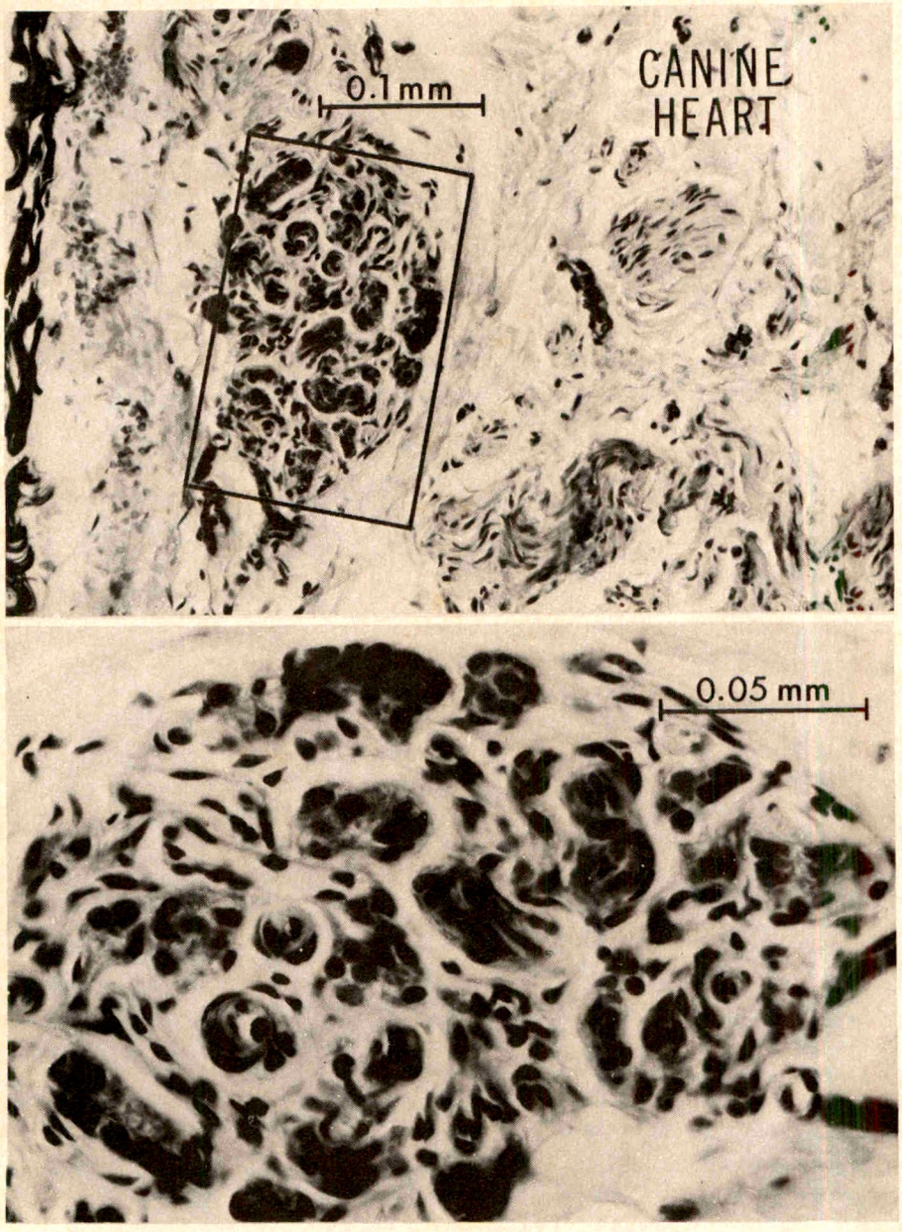

FIGURE 2. Photomicrographs illustrating the coronary chemoreceptor of the dog. The **boxed area** (at top) is shown at higher magnification below. Actual magnification is indicated by **reference bars.** (Goldner trichrome stain.)

carotid and femoral circulations show a moderate initial vasoconstriction. Pulse pressure consistently widens directly at the peak of the aortic hypertension, demonstrating the brevity of systemic vasoconstriction and the onset of a marked increase in cardiac output. Possible special significance of the sparing of the coronary and pulmonary arteries will be discussed later.

Contractile responses: Inotropic responses are exclusively positive for the ventricular myocardium, and there is a more pronounced effect in the right than in the left ventricle (Fig. 4). Atrial inotropic responses are mixed, with concomitant stimulation and suppression due to simultaneous sympathetic and vagal influences, respectively. The mixed atrial response can be separated by prior treatment with atropine, after which there is exclusively a positive inotropic effect (Fig. 5).

Electrophysiologic effects: Chronotropic and dromotropic effects during the cardiogenic hypertensive chemoreflex are also mixed autonomic responses, in part but not entirely due to secondary effects of the hypertension. For example, bradycardia and heart block during the first few seconds of the response are due both to the chemoreflex itself and to a secondary baroreflex elicited when the sudden hypertension activates pressor receptors. Atrial fibrillation is sometimes produced briefly during the onset of the cardiogenic hypertensive chemoreflex, as a result of the mixed vagal and sympathetic influences on the atria. Most of these separate components of the electrophysiologic responses can be either eliminated or quantified by the selective administration of either atropine or propranolol into the sinus nodal artery or the atrioventricular nodal artery.[16] For example, when atropine is used selectively to exclude vagal response by the sinus node, the brief heart block is more prominent and easily assessed (Fig. 6). Finally, transient alterations of both atrial and ventricular repolarization accompany all the changes in cardiac rhythm and conduction.

Blocking the reflex: Cutting or cooling the vagi blocks the cardiogenic hypertensive chemoreflex. It is usually necessary to cut both vagi, although in rare examples cutting the left vagus alone is sufficient.[10] Cyproheptadine can be used for pharmacologic blockade because of its antiserotonin action on the chemoreceptor,[11] and not some extracardiac effect, for example in the brain. The cyproheptadine blockade is competitive in nature and at the site of initiation of the reflex and can be overcome by the administration of larger concentrations of serotonin. The fact that methysergide fails to block the reflex, although it is known to be an effective antagonist to a number of different responses to serotonin, demonstrates that the

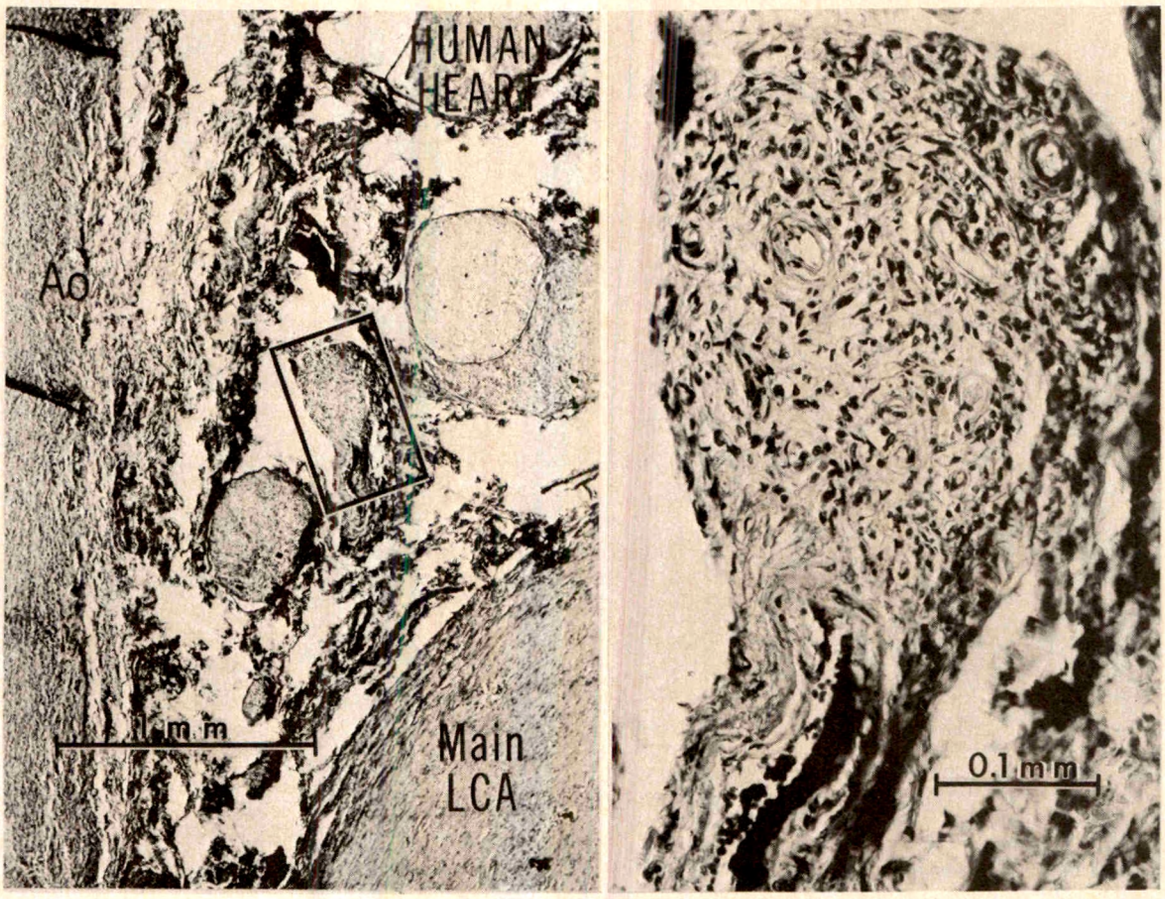

FIGURE 3. Photomicrographs of human coronary chemoreceptor. **Boxed area (left)** is seen at higher magnification at the **right.** Note the chemoreceptor artery arising from the main left coronary artery (LCA). Other neural elements abound in this region. Ao = aortic pressure.

coronary chemoreceptor differs in this respect from those other serotonin receptors.

Dose response and tachyphylaxis: After initial experiments in which the effects of serotonin were compared when injected into small branches of the left coronary artery and when injected into the left atrium, we have found[3] that the only difference in response was the longer duration of hypertension after the left atrial injection, and this was caused by the delivery of some serotonin downstream to the adrenal glands. The initial reflex response is the same, and left atrial injections are simpler and more convenient and eliminate the danger of inadvertent denervation. With either route of administration, intraatrial or intraarterial, there is a dose-related responsiveness, smaller concentrations (10 to 25 μg) of serotonin causing distinct but less profound hypertension. A maximal hypertensive reflex response can be elicited with 2 ml of serotonin (100 μg/ml) quickly injected into the left atrium. There is no tachyphylaxis in the serotonin response, repeated injections continuing to elicit similar hypertensive responses. The normal concentration of serotonin in shed blood is about 1 μg/ml.[17] When we consider that virtually all circulating serotonin is bound to platelets, the amount of serotonin to be expected in 1 ml of platelets (were they to be aggregating as a solid mass within a coronary artery) would be well over 1,000 μg. It seems likely, therefore, that the concentrations of serotonin we are

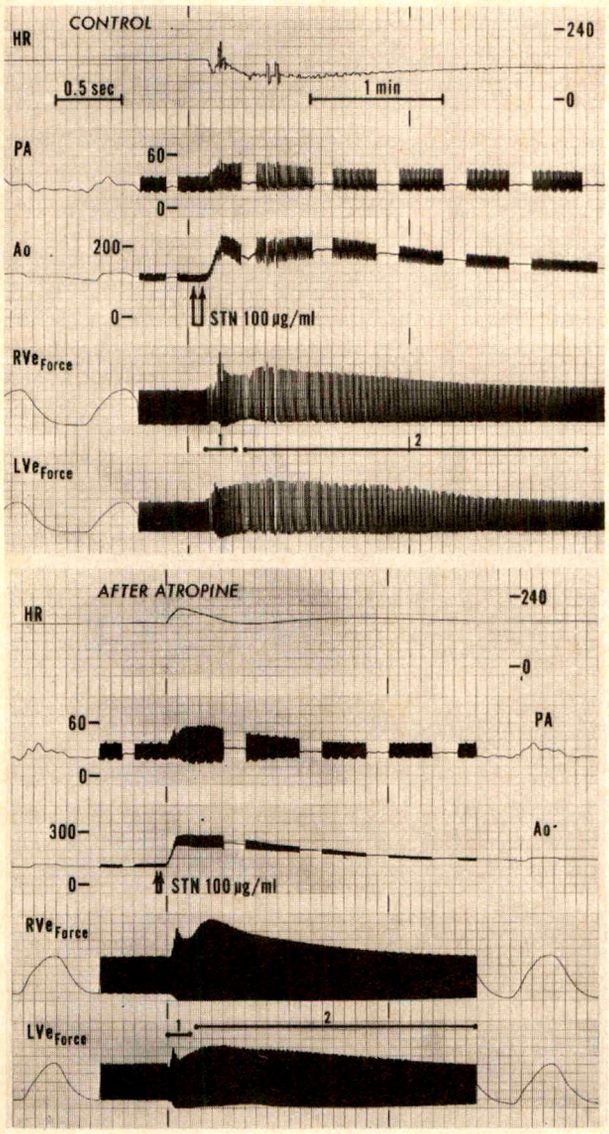

FIGURE 4. Upper panel, during the cardiogenic hypertensive chemoreflex produced by serotonin (STN) there is a positive inotropic response by both the right and the left ventricles (respective strain gauges marked RVe and LVe). Pulmonary arterial (PA) pressure increases slightly because of increased vigor of right ventricular contraction but not vasoconstriction in the pulmonary vessels. Two phases of the aortic hypertensive response are marked 1 and 2; the second is in part due to serotonin reaching the adrenal glands. **Lower panel,** atropine eliminates the reflex bradycardia. Ao = aortic pressure; HR = heart rate. (Reprinted from Urthaler et al.[3] by permission of the American Heart Association, Inc.)

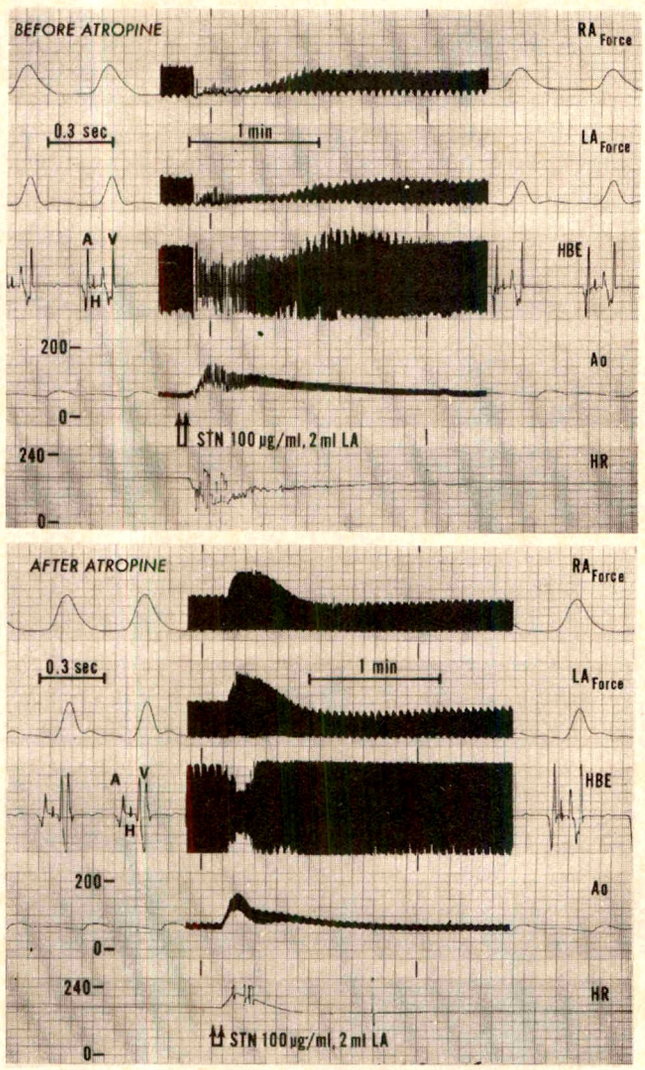

FIGURE 5. The negative inotropic response by right (RA) and left (LA) atrial myocardium during the cardiogenic hypertensive chemoreflex (**upper panel**) is reversed to a positive response by the administration of atropine (**lower panel**). HBE is an electrogram from the region of the His bundle. STN = serotonin. (Reprinted from Urthaler et al.[3] by permission of The American Heart Association, Inc.)

using experimentally are well within the range that may be present early in coronary thrombosis, and more will be said of this later.

Other possible substances: Of course, other vasoactive substances, such as bradykinin, histamine and certain prostaglandin fractions, are carried by and released from platelets. Furthermore, the existence and the nature of "sensory neurotransmitters"[18,19] have been the subject of continuing debate, both acetylcholine and norepinephrine (the usual efferent neurotransmitters) being candidate substances. We found none of these compounds effective in engaging the cardiogenic hypertensive chemoreflex. Certain alkaloids such as lobeline and nicotine, which do not occur naturally in the mammalian circulation, will produce the reflex hypertension, but the most powerful substance we have yet investigated is serotonin.

Possible Clinical Significance of the Cardiogenic Hypertensive Chemoreflex

Although the chemoreceptor tissue and its left coronary blood supply are impressively similar in both human and canine hearts, there is as yet no direct proof that the cardiogenic hypertensive chemoreflex exists in man. However, a body of indirect evidence suggests that it may. Much of this interpretation is based on the fact that platelet aggregations can and do form within the human left coronary artery, that such aggregations would release serotonin and that this serotonin could enter the arterial branch supplying the chemoreceptor.

Coronary artery disease: If one were to choose the most likely clinical circumstances in which platelet aggregations would be forming in the coronary arteries, they are probably coronary atherosclerosis and ischemic heart disease. Nearly half a century ago Sir Thomas Lewis[20] recognized that in some patients with angina pectoris new hypertension with palpitations develops, a condition for which he coined the phrase "autonomic storms." Shortly thereafter, Levine and Ernstene[21] demonstrated that such hypertension preceded rather than followed the onset of anginal pain, thus excluding the possibility that the hypertension was an emotional or psychogenic response. Actually, the type of hypertension often seen in patients very early in the course of acute myocardial infarction or during angina pectoris is frequently too severe to be readily attributable to emotions or anguish, *diastolic* levels sometimes being 160 mm Hg or more. Paroxysmal occurrence of such severe hypertension is sometimes misdiagnosed as pheochromocytoma; in 1967 Horwitz and Sjoerdsma[22] warned against this diagnostic pitfall. In discussing their findings in four patients with severe hypertension occurring paroxysmally in association with angina and myocardial infarction, they speculated that the source of such hypertension might reside in some special neuroreceptor within the heart itself.

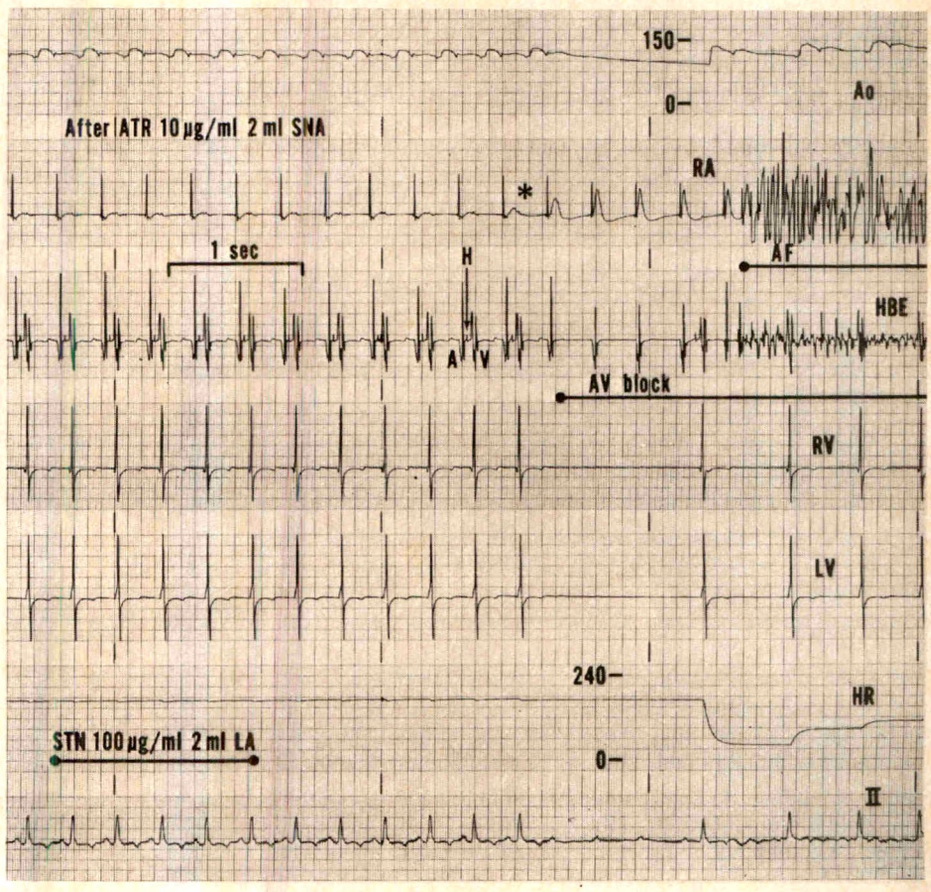

FIGURE 6. At the onset of the cardiogenic hypertensive chemoreflex the negative dromotropic effect can be unmasked by blocking the vagal response of the sinus node with atropine (ATR) selectively administered into the sinus nodal artery (SNA). At the asterisk an elevation of the atrial repolarization (P-Tp) segment begins, followed by transient atrial fibrillation, both due to reflex influence on other portions of atrial myocardium. AF = atrial fibrillation; Ao = aortic pressure tracing; AV = atrioventricular; HBE = His bundle electrogram; II = lead II of the electrocardiogram. RA, RV and LV represent local electrograms from the right atrium and from the right and the left ventricle, respectively.

Acute anterior versus posterior myocardial infarction: Because of the anatomic location of the coronary chemoreceptor, and because an opposite hemodynamic and electrophysiologic response is seen during acute posterior myocardial infarction, we initially suspected that new hypertension during acute myocardial infarction might be more prevalent with anterior infarcts. However, this did not prove to be the case.[13] New hypertension occurs equally often with either anterior or posterior myocardial infarction. Realizing that multiple coronary disease was the usual situation in any patient with acute myocardial infarction, we then examined the available coronary arteriograms in this group of patients to see whether any patient with new hypertension had an entirely normal proximal left coronary circulation, and none did. Thus, new hypertension was no more frequent with anterior than with posterior infarction, but every patient with new hypertension had disease in the proximal left coronary circulation. Ultimately, it will be necessary to have more direct correlations in such cases, particularly at necropsy examination of any patients who die after initially exhibiting new hypertension.

Severity of the hypertensive response in some patients with acute myocardial infarction can be alarming, but perhaps should not be. In our study of such patients[13] we found no increase in either morbidity or mortality among those who had new hypertension. That chronic hypertension worsens the prognosis is a separate and well documented matter. If the new hypertension is a human response to local release of serotonin from platelets aggregating on the wall of the main left coronary artery, a sudden marked increase in central aortic pressure could have a protective effect by dislodging the clot while it is still friable and not fully formed. This would be an exceptionally valuable protective response against an especially dangerous type and location of coronary occlusion. The absence of constriction of either the coronary or the pulmonary circulation during the reflex is conspicuous and may be additionally of special survival value under these circumstances.

Postoperative hypertension: A different but possibly related clinical phenomenon may be the hypertension increasingly recognized to occur after saphenous vein bypass coronary surgery.[23–27] This type of hypertension may be more frequent with bypass to the left coronary artery.[24] Although there is some debate as to the mechanism of such postoperative hypertension (some investigators found elevated angiotensin levels[25] while others did not[26,27]), Tarazi et al.[23] have offered impressive evidence for neural mediation of the hypertension. We have previously speculated[28] that this type of postoperative hypertension—as well as that reported to occur after aortic valve surgery[29]—may be related to cardiogenic pressor reflexes; these may originate from various sites in different cases including the coronary chemoreceptor in some[28] and in other reflexes with sympathetic afferents.[23] The event triggering the coronary chemoreflex could be direct injury or irritation of the chemoreceptor, the secondary aggregation of platelets caused by local surgical trauma, or even the release of serotonin into the blood from platelet damage during pump bypass. Postoperative new hypertension in patients undergoing these and similar types of cardiac operations deserves the active investigative attention it is now receiving. If it proves to be a human example of the cardiogenic hypertensive chemoreflex, its ready interdiction or reversal with cyproheptadine is likely, although whether such therapy should be undertaken is a separate question. It will first be necessary to know whether the postoperative hypertension afforded some protective or beneficial influence.

Arteritis and hypertension: Patients with polyarteritis nodosa or with Takayasu's arteritis frequently have hypertension, which is sometimes severe. There is abundant reason to anticipate such hypertension because of the known aortic constrictive effects of Takayasu's arteritis and the renal arterial effects of either disease. However, to these known explanations we should perhaps add involvement of the coronary chemoreceptor as a contributing influence, since there is no reason to expect that this nutrient vessel or the coronary artery proximal to its origin should be somehow spared from at least random involvement by any arteritis.

Cardiogenic shock and essential hypertension: Whether the coronary chemoreceptor is tonically active is unknown, although no afferent neural traffic is visible experimentally[11] except after serotonin stimulation. Low grade activity in such afferent nerves, if it exists, may be missed with our present methods. Such a tonic influence could have two opposite but equally important clinical consequences. Its loss during acute myocardial infarction, which would of necessity be associated with a proximal left coronary obstruction, may be a compounding problem in so-called cardiogenic shock. In the opposite direction, chronic overactivity from the coronary chemoreceptor could be a contributing factor in the pathogenesis of unexplained or "essential" hypertension. There is little apparent therapeutic value to knowing that chemoreceptor loss during massive myocardial infarction may compound the shock, at least in our present state of knowledge. On the other hand, the possible contribution of the chemoreflex in the pathogenesis of essential hypertension may have great clinical value and this may represent a treatable factor.

Unexplained cardiac hypertrophy: Finally, there is an even more speculative but equally attractive hypothesis to consider relative to left ventricular hypertrophy of unexplained cause. During the course of other studies having to do with carotid body size, Heath et al.[30] discovered that the presence of a large carotid body correlated positively with the presence of a large left ventricle, and that this did not depend on the existence of chronic hypertension. Others[31] have confirmed this observation, which remains unexplained. Given the histologic similarity of the coronary chemoreceptor and the carotid body, we should consider whether the former may have some function other than pressure regulation and associated mechanical and electrophysiologic effects. It is known, for example, that chronic administration of norepinephrine in concentrations less than

those that influence blood pressure can lead to left ventricular hypertrophy.[32] Furthermore, the left ventricular hypertrophy seen in some hypertensive rats can be dissociated from the hypertension, hypertrophy occurring even in the presence of normal blood pressure.[33] There are many other unexplained examples of cardiac hypertrophy, often lumped in the meaningless category of cardiomyopathy. Just as it has been shown that the carotid body can elaborate a hormone influencing erythropoiesis,[34] a heretofore unsuspected function, it is reasonable to question whether the coronary chemoreceptor elaborates some substances influencing ventricular hypertrophy. Alternatively, continued low level activity of the chemoreceptor could chronically release reflexly small amounts of norepinephrine in the ventricular myocardium and lead to its hypertrophy, as has been shown with systemic administration of subpressor amounts of norepinephrine.[32]

If unexplained hypertrophy of the heart or unexplained hypertension or both can somehow be related to functions of the coronary chemoreceptor, we would still need to determine whether such function requires greater chemoreceptor mass or a different kind of chemoreceptor or whether it represents overactivity or malfunction of normal size and structure of the chemoreceptor. We would also need to determine the source or cause for the necessary continued activation of the coronary chemoreceptor. All these hypothetical considerations are susceptible to investigation and may provide a fascinating new perspective on many old but important questions in experimental and clinical biology.

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Positive Feedback Sympathetic Reflexes and Hypertension

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A pressor reflex that can be elicited from the thoracic aorta in conscious dogs is described. Distension of the aorta excites sympathetic afferent fibers and results in an increase in arterial blood pressure because of increased sympathetic outflow to the heart and blood vessels. The reflex center for this positive feedback mechanism is located in the spinal cord and, when the reflex is activated, it can modulate other negative feedback control systems.

This paper will summarize current knowledge of a pressor reflex that can be elicited from the thoracic aorta through excitation of the sympathetic mechanosensitive endings located therein. This pressor reflex constitutes a positive feedback mechanism that interacts with the sinoaortic and other negative feedback control systems in the regulation of arterial blood pressure.

"The conception of a reflex . . . embraces that of at least three separable structures, an *effector* organ . . . ; a *conducting nervous path* . . . ; and an *initiating organ or receptor* whence the reaction starts."[1] The initiating organ or receptor for this pressor reflex is the descending thoracic aorta with its sympathetic sensory innervation. We[2] recently carried out an electrophysiologic study of afferent sympathetic nerve fibers, myelinated or unmyelinated, with aortic sensory endings. These sympathetic mechanoreceptors appeared to be affected by a variety of hemodynamic interventions, which indicated that the pulsatile stretch of the aortic wall was probably the most effective natural excitatory stimulus.

Experimental Observations

Aortic Stretch and Afferent Sympathetic Activity

The properties of these mechanoreceptors of the thoracic aorta were studied after cats had been killed and a large saline-filled latex balloon introduced into the aorta through the left ventricle. Figure 1 shows a postmortem study of the activity in an afferent sympathetic unmyelinated fiber during progressive distension of the aortic segment containing the sensory endings. The highest impulse frequencies were attained concomitant with the rising phase of the stimulus, followed thereafter by an adapted discharge; there was a proportionality between the intensity of the stimulus and both the "dynamic" and the "static" component of the receptor response. The pressure used to distend the balloon was an index of aortic wall stretch, because we had observed that such a pressure was approximately linearly related to the external aortic dimension measured with ultrasonic techniques.[3]

In short, we had found a vascular site from which it was possible to obtain, with a mechanical stimulus, graded excitations of part of that afferent sympathetic path that connects the cardiovascular system with the spinal cord. Although many believe that these afferent fibers are normally silent and signal only visceral pain, in fact the afferent sympathetic fibers with cardiovascular sensory endings, both myelinated

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and unmyelinated, have a tonic impulse activity, are extremely sensitive to normal hemodynamic events[4–6] and are thus likely to subserve a tonic regulatory function.[5] Moreover, concerning the problem of visceral pain, we recently performed experiments to test the possible exclusive nociceptive function of ventricular sympathetic unmyelinated afferent fibers. We found that intracoronary injections of bradykinin or myocardial ischemia always increased the impulse activity of fibers that were already firing spontaneously but never recruited silent fibers.[7] The peripheral mechanism for cardiac pain, therefore, seems to be the result of massive excitation of sympathetic afferent fibers and not of specific excitation of pure nociceptors that have no background activity.[8] Thus, the aortic sympathetic afferent fibers, which have a tonic impulse activity, are unlikely to have an exclusive nociceptive function. From these considerations it seemed plausible to hypothesize that the thoracic aorta could constitute a reflexogenic area.

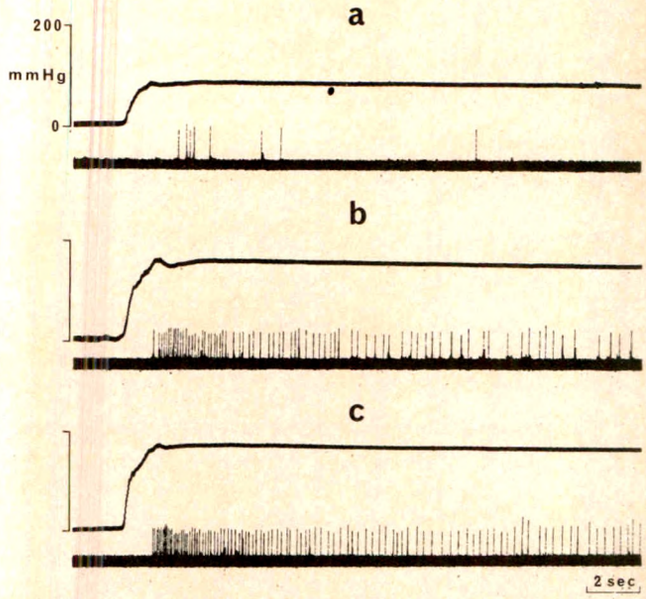

FIGURE 1. Activity of an afferent sympathetic unmyelinated nerve fiber (group C) with receptive field located in the thoracic aorta. Effects of stretching aortic wall by distending a latex balloon located in the aorta postmortem (see text). **Top tracing,** pressure applied to the distending balloon; **bottom tracing,** nervous activity. Panels **a** to **c** show progressive increases in distending pressure. (Malliani and Pagani, unpublished observations.)

Hemodynamic Effects of Aortic Stretch

A metal cannula covered by an inflatable rubber cylinder was used to stretch the descending thoracic aorta without obstructing its flow (Fig. 2, left). Another advantage of this approach is the paucity or possible absence of afferent vagal fibers innervating this part of the aorta.[9] The experiments were performed on anesthetized cats subjected to vagotomy with both common carotid arteries occluded, with or without a section of the spinal cord at the level of the first cervical vertebra.[10] Aortic stretch induced significant increases in arterial blood pressure, heart rate and maximal rate of increase in left ventricular pressure (dP/dt_{max}) (Fig. 2). Blockade of alpha adrenergic receptors with phenoxybenzamine abolished the pressor response but not the increase in heart rate and dP/dt_{max}, whereas beta adrenergic blockade with propranolol drastically reduced the increase in heart rate and dP/dt_{max} but not the pressure response. These responses were abolished by infiltrating the walls of the thoracic aorta with Xylocaine®; hence, they were reflex in nature. In this way the *initiating organ* and the *effector* function of the reflex were identified.

The finding of this pressor reflex was not surprising because for years we had had evidence that the hemodynamic reflexes mediated by the afferent sympathetic fibers were mainly excitatory. However, the increase in

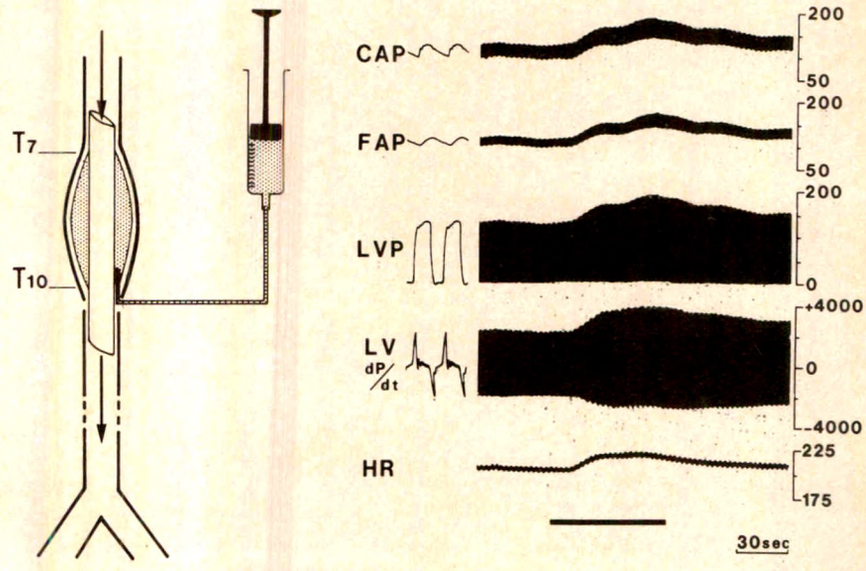

FIGURE 2. Effects of stretching and decreasing thoracic aorta in a vagotomized cat with an intact central nervous system and both common carotid arteries occluded. **Left,** schematic drawing of the aortic cannula. **Right,** carotid arterial pressure (CAP); femoral arterial pressure (FAP); left ventricular pressure (LVP) (all in mm Hg); rate of change of left ventricular pressure (LV dP/dt) (mm Hg/sec); heart rate (HR) (beats/min). On the left of each section are high-speed records of each variable. The aortic stretch is indicated by a **bar.** (Modified and reproduced, by permission of the American Heart Association, Inc., from Lioy et al.[10])

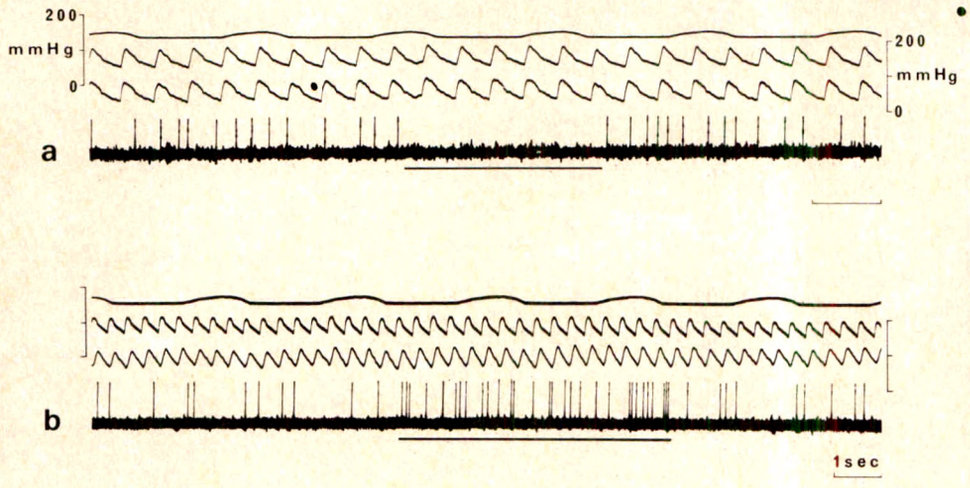

FIGURE 3. Effects of stretching (marked by a **bar**) the aortic walls (as schematized in Fig. 2) on the discharge of two different (a) and (b) sympathetic preganglionic fibers isolated from the cut central end of the third left thoracic sympathetic ramus communicans. Tracings represent, **from top to bottom,** the endotracheal pressure (inflation upwards), the carotid and femoral arterial blood pressure and the nervous recording. (Reproduced, by permission, from Pagani et al.[17])

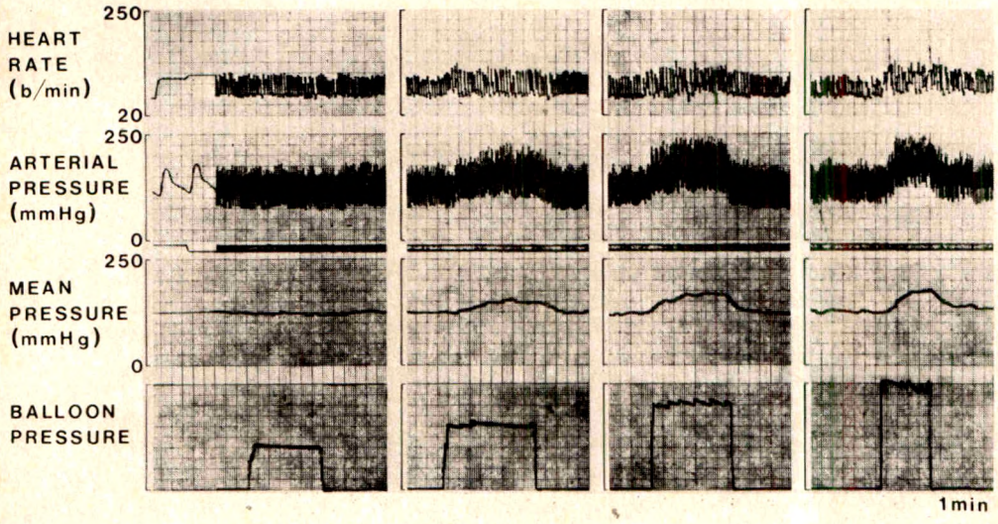

FIGURE 4. Effects of a progressively increasing aortic stretch on arterial pressure and heart rate in a conscious dog. The distending balloon pressure, which obviously does not correspond to the pressure effectively applied to the aortic walls, is displayed in the **bottom tracing** as an index of the progressive stretch.

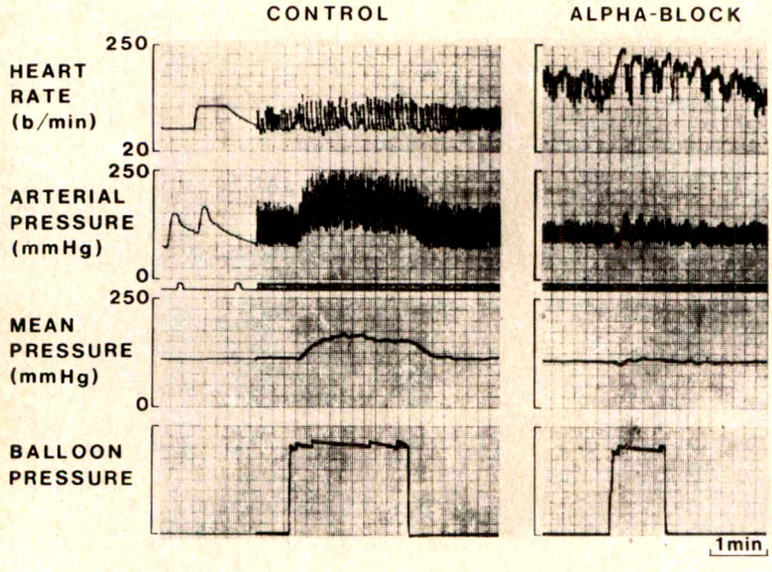

FIGURE 5. Effects of alpha adrenergic blockade on the cardiovascular response to aortic stretch, indicated by the **bottom tracing,** in a conscious dog. Note that after alpha blockade (phentolamine 1 mg/kg intravenously) the pressor response is abolished, but the reflex tachycardia is increased.

arterial blood pressure,[11] myocardial contractility[12] and heart rate[13] were obtained with electrical or chemical stimulation, that is, with stimuli devoid of physiologic significance. We had also been studying the impulse activity of single fibers isolated from the efferent limb of the sympathetic circuit. These electrophysiologic experiments, in which natural stimuli were used to elicit the reflex responses,[14–17] provided detailed information on the specificity and sensitivity of these sympathosympathetic reflexes, but a clear understanding was still elusive.

A similar mechanical stretch of the thoracic aorta appears (Fig. 3) to be capable of promptly modifying the impulse activity of two different sympathetic preganglionic fibers isolated from the same thoracic, largely cardiac, outflow: Discharge of one fiber was inhibited whereas discharge of the other was excited. All of these fibers were excited when a stimulus was applied mainly to the heart.[17] We advanced the hypothesis[18] that in sympathosympathetic reflexes the predominant excitation would be recorded with outflows originating from the same spinal segments directly excited by the impinging afferent activity whereas inhibitory components would progressively be present in the reflex activity of more distant outflows. Therefore, cardiocardiac reflexes would mainly be excitatory whereas a reflex elicited from the descending aorta and directed to the heart would possess both excitatory and inhibitory components. Indeed, subsequent reports[19,20] demonstrated the possibility of obtaining hemodynamic biphasic responses by stimulating afferent sympathetic fibers with various electric parameters.

In conclusion, considering the complexity of the electrophysiologic findings, the unnatural stimuli used in the hemodynamic experiments, the anesthesia and the extensive surgery in the acute preparations, we could confidently affirm the existence of neural mechanisms that could yield pressor reflexes; however, we had no proof of their existence in the intact unanesthetized animal.

Aortic Stretch in the Conscious Dog

Under general anesthesia and aseptic conditions, dogs were instrumented with a pressure catheter, and a 7 cm metal cannula covered by an inflatable rubber balloon was positioned in the descending thoracic aorta.[21] After a recovery period of 1 to 2 weeks, the implanted balloon was inflated, causing distension of a short segment of the aorta in the conscious dog. This stretch, in the absence of pseudoaffective reactions, produced a sustained and significant ($P < 0.02$) increase in mean arterial pressure (18 ± 2 from 107 ± 6 mm Hg) and heart rate (17 ± 4 from 108 ± 5 beats/min) (mean ± standard error). Above a given threshold level, progressive increases in the pressor response were obtained by augmenting the distension (Fig. 4). The reflex nature of the pressor response was proved by its disappearance after alpha adrenergic blockade (phentolamine, 0.5 mg/kg body weight intravenously) (Fig. 5). The reflex tachycardia was abolished by combined vagal and beta blockade (atropine or scopolamine, 0.2 to 0.3 mg/kg and propranolol, 1 mg/kg, intravenously).

The possibility that this sympathetic reflex might interact with baroreceptor mechanisms was also investigated, because such an interplay was suggested by a previous electrophysiologic study.[22] The slope of the regression of the R-R interval on the systolic pressure increase induced by 50 μg/kg of phenylephrine intravenously was used as an index of baroreflex sensitivity. This regression was obtained in both the presence and the absence of aortic stretch, which produced a significant reduction in baroreflex sensitivity (45 percent from 20 msec/mm Hg).

The adequacy of the stimulus must be considered. Stretches similar to those used in the experimental trials increased the aortic diameter in postmortem control experiments by about 10 percent; this increase is in the range of changes in diameter accompanying physiologic increases in arterial pressure.[23] Also, a static stretch should be less effective in eliciting the dynamic component of the mechanosensitivity of the receptors with respect to comparable but rhythmic wall expansions induced by arterial pressure pulses. Finally, the shortness of the aortic segment that was distended should be considered. All of these factors point to a remarkable potentiality for these reflexes.

Several additional comments on the behavior of conscious dogs during aortic stretching are indicated. Sutton and Lueth[24] in 1930 had already reported the results of experiments in unanesthetized dogs designed to test the hypothesis of an aortic origin of anginal pain: stretching of the ascending aorta produced no evidence of pain. In anesthetized animals the same stimulus sometimes produced hypertension. In our experiments, the magnitude of the stretch was progressively increased to obtain a maximal pressor response in the absence of movements and pseudoaffective reactions. That appropriate amount of stretch was found to remain constant throughout the period of study. A further increase in stretching induced restlessness similar to that observed during excessive increases in arterial pressure induced by pressor drugs.

Discussion and Hypothesis

Our experiments revealed excitatory reflexes mediated by cardiovascular sympathetic afferent fibers that exhibit positive feedback characteristics. In fact, an increase in mean aortic pressure likely to excite the aortic mechanoreceptors elicited an increase in systemic arterial pressure through a sympathetic reflex directed to the cardiovascular system (Fig. 6).

These pressor reflexes should obviously be conceived as part of those complex regulatory mechanisms that are the result of multiple and independent peripheral loops and various levels of central integration. Negative feedback mechanisms thus seem quite often to be the effective controllers in overall cardiovascular regulation. However, even in this case, positive feedback mechanisms could be of paramount importance in determining the range of operation, the gain and the stability.

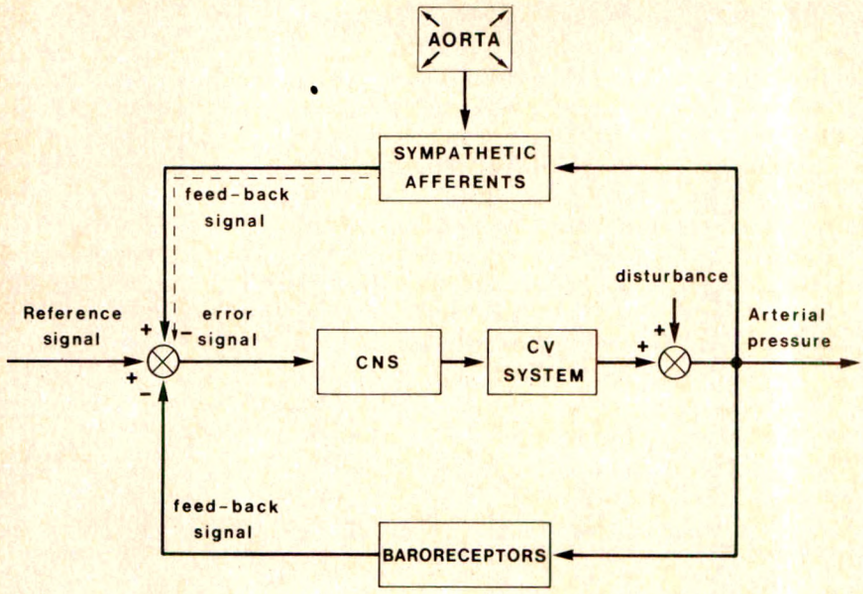

FIGURE 6. Schema of suggested mechanisms underlying nervous control of arterial blood pressure regulation. Baroreceptors are indicated as the example of receptors that activate negative feedback mechanisms. The coexistence of inhibitory components in reflexes mediated by sympathetic afferents is represented by the **broken line.** CNS = central nervous system; CV = cardiovascular.

There are however, physiologic conditions in which the efferent sympathetic activity seems to escape any restriction, as in exercise. Arterial hypertension, as a disease of regulation, could partly be the result of an increased sympathetic efferent tone. This increase, according to our hypothesis, may depend not only on an augmented central command but also on the peripheral action of sympathosympathetic loops exhibiting positive feedback characteristics.

The spinal arc, which is considered the elementary basis of the somatic nervous system, is still regarded as an unnecessary simplification in the study of the sympathetic nervous system. However, the mechanisms that produce a sustained increase in sympathetic efferent activity may be similar to those that in the decerebrate animal are responsible for rigidity or spasticity. Sherrington[1] found that spasticity was abolished by deafferentation. It was thus proved that an augmented central command was incapable in itself of causing a sustained increase in the postural tone but that a peripheral loop was necessary for maintenance of the phenomenon. This hypothesis may perhaps stimulate a new way of interpreting the complexity of clinical medicine.[25,26]

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Possible Role of Cardioaortic Reflexes in Postcoronary Bypass Hypertension

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A study of hemodynamic and humoral characteristics of postcoronary bypass hypertension has been pursued in 85 patients in the immediate postoperative period. Paroxysmal hypertension developed in 69 of these patients. None of the 85 patients had a history of hypertension before operation. Hemodynamic evaluation demonstrated that the increase in blood pressure was associated with an elevation in systemic vascular resistance and a rapid heart rate. The increase in mean arterial pressure correlated significantly with the change in plasma catecholamine levels ($r = 0.50$, $P < 0.05$). There was no significant change in cardiac output. Changes in plasma renin activity showed no correlation with the increase in blood pressure. Average values of plasma renin activity on sequential determinations were not significantly different either in those who remained normotensive or in those who became hypertensive. Similarly, blood volume did not seem to play an important role. Baroreceptor sensitivity appeared blunted in both normotensive and hypertensive patients. The increase in systemic catecholamines associated with the increase in blood pressure suggested a sympathetic overdrive. This was further supported by the control of hypertension in 81 percent of patients by unilateral stellate block. The reduction in pressure consequent to the block was associated with a reduction in systemic vascular resistance ($P < 0.025$). Heart rate slowed slightly but significantly ($P < 0.01$) after stellate block irrespective of the effect on blood pressure whereas cardiac output did not change significantly. The results suggest that postcoronary bypass hypertension could be due to an afferent sympathetic reflex originating from the heart, great vessels or coronary arteries.

Although postcoronary bypass hypertension is now well recognized, its cause is still a subject of debate. The seriousness of the complications that it can precipitate[1–3] mandates the study of its characteristics and pathogenesis to delineate rational therapy or plan effective prevention. In this paper we summarize our continuing experience with the study of its hemodynamic and humoral aspects in 85 patients after coronary bypass surgery.

The evidence gathered to date continues to point to a sympathetic reflex mechanism originating probably from the heart and great vessels. This conclusion, which was suggested by our initial hemodynamic studies,[4] was subsequently substantiated by results of unilateral stellate block.[5] These initial observations were extended to a larger number of patients, and sequential determinations of plasma renin activity and circulating catecholamines have now been added to hemodyamic investigations.

Methods

Study patients: Eighty-five unselected patients, 7 women and 78 men, were studied after coronary bypass surgery. All were known to be normotensive preoperatively. Their ages ranged from 33 to 65 years. Coronary artery disease had been recognized from weeks to years before operations and confirmed in all instances with coronary arteriography. Left ventricular end-diastolic pressure

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TABLE I

Serial Hemodynamic Measurements in Groups I and II*

	Group I (no. = 7)			Group II (no. = 10)		
	C_1	C_2	$P^\dagger$	C	HT	$P^\dagger$
SBP (mm Hg)	114 ± 2.1	110 ± 2.1	NS	132 ± 4.0	173 ± 5.9	<0.001
DPB (mm Hg)	68 ± 3.2	62 ± 2.8	NS	78 ± 2.5	101 ± 2.4	<0.001
HR (beat/min)	92 ± 3.6	90 ± 1.8	NS	102 ± 3.7	103 ± 3.0	NS
CI (liters/min per m^2)	2.13 ± 0.19	2.15 ± 0.16	NS	2.66 ± 0.25	2.73 ± 0.17	NS
SI (ml/m^2)	23 ± 1.9	24 ± 2.1	NS	26 ± 2.8	27 ± 2.1	NS
TPR (units·m^2)	41 ± 3.3	38 ± 3.4	NS	38 ± 2.5	47 ± 2.9	<0.001

* Group I = normotensive patients; Group II = patients who became hypertensive.
† Probability (*P*) values based on paired *t* test.
C = control cardiac output; C_1 = first control cardiac output study; C_2 = second control cardiac output study (4 to 6 hours after recovery); CI = cardiac index; DBP = diastolic blood pressure; HR = heart rate; HT = cardiac output study performed during the hypertensive episode; NS = not significant; SBP = systolic blood pressure; SI = stroke index; TPR = total peripheral resistance.

Results

Part I: Study of Hypertensive Phase

Hemodynamics: Repeated hemodynamic studies in normotensive patients (Group I) revealed a remarkable stability of indexes during the 4 hours of observation (Table I). In contrast, the hypertensive episode in all patients of Group II was associated with a definite increase in total peripheral vascular resistance (P <0.001) (Table I). Despite the increase in blood pressure, the heart rate remained unchanged. The patients who were hypertensive from the start (27 patients in Group III) showed hemodynamic characteristics similar to those determined during the hypertensive phase of patients in Group II (Table II).

Throughout the study, the central venous pressure in all patients and the left atrial pressure (in those patients for whom it was available) remained within normal limits; there was no significant increase in either pressure during the hypertensive episode. Hematocrit and hemoglobin levels did not show significant variations during this period (P >0.5) and there was no correlation between minor variations seen in the hematocrit level and in cardiac indexes (r = 0.073, P >0.05).

Test of baroreceptor sensitivity (Table III): The slope of the correlation between the decreasing systolic blood pressure after intravenous nitroglycerin and the duration of the succeeding R-R interval[7,8] was not significantly different between normotensive and hypertensive patients. In five patients, the slope was measured in both the normotensive and the hypertensive phase; no consistent changes between the two were observed. The slope increased in one patient, decreased in two and was not significantly changed in two. In all patients, this index of baroreceptor sensitivity was lower than expected for this age group.[11]

Plasma renin activity and plasma catecholamines: Plasma renin activity was determined in 20 patients. Five of these 20 patients were normotensive and in 15 hypertension developed. There was no significant change in plasma renin activity either among those who remained normotensive or among those who became hypertensive (Fig. 2). Also, there was not significant correlation between the increase in mean arterial pressure and the change in plasma renin activity (r = 0.21). Control values of plasma renin activity in the normotensive and hypertensive groups were not significantly different (2.96 ± 1.14 versus 5.01 ± 1.83 ng/ml; P = not significant). In contrast were the findings with the plasma catecholamine levels; they did not change significantly in those who remained normotensive but showed a tendency to increase in hypertensive patients with the elevation in blood pressure (Table IV). A significant correlation was found between the increase

TABLE II

Hemodynamic Characteristics of Postcoronary Bypass Hypertension

	Group II (no. = 10)	Group III (no. = 27)
SBP (mm Hg)	173 ± 5.9	177 ± 5.2
DBP (mm Hg)	101 ± 2.4	100 ± 2.45
HR (beats/min)	103 ± 3.0	96 ± 3.25
CI (liters/min per m^2)	2.78 ± 0.17	2.50 ± 0.21
SI (ml/m^2)	27 ± 2.1	26 ± 2.0
TPR (units·m^2)	47 ± 2.9	57 ± 4.6

Abbreviations as in Table I.
Values listed under Group II are those obtained during the hypertensive phase; none was significantly different from the corresponding value in Group III (patients who were hypertensive on return to recovery room).

TABLE III

Baroreceptor Sensitivity* in Patients After Coronary Bypass Surgery

	Normotensive Patients (no. = 9)	Hypertensive Patients (no. = 8)	P
Age (yr)	52 ± 2.52	51 ± 1.72	
SBP (mm Hg)			
Control	137 ± 4.51	178 ± 3.29	<0.001
Δ Post NTG	−44 ± 4.05	−41 ± 5.91	NS
Slope (msec/mm Hg)	0.8618 ± 0.23	0.6501 ± 0.16	NS

* Baroreceptor sensitivity determined from changes in R-R interval consequent to reduction of systolic blood pressure (SBP) by intravenous nitroglycerin (NTG). P = probability.

determined before ventriculography ranged from 4 to 32 mm Hg. Coronary arterial lesions were bypassed by either saphenous vein grafts or anastomosis of the left internal mammary artery. Surgery involved one to three coronary arteries. Anesthetic technique and agents used were the same in all patients as previously described.[1,6] After return to the recovery room, the patients were kept sedated and adequately ventilated; both arterial and central venous pressure were continuously monitored.[4] Left atrial pressure measurements were available only in those patients who at operation had a catheter placed into the left atrium at its junction with the superior pulmonary vein.[6]

A hypertensive episode was defined as a sustained increase above preoperative levels by at least 20 mm Hg for the diastolic blood pressure and 30 to 40 mm Hg in systolic levels,[1] provided that: (1) this rise was not reversed by simple sedation, and (2) there was no evidence of hypoxia, hypercarbia, shivering, fighting the ventilator or intolerance of the endotracheal tube. Included as hypertensive episodes, therefore, were only those instances in which a high blood pressure level was maintained for at least 10 to 20 minutes despite proper sedation.[1,3] On the basis of this definition, patients could be classified into three groups: (1) those who were normotensive on reaching the recovery room and who remained so throughout the observation period (16 patients); (2) those who were normotensive when they reached the recovery room and later had a hypertensive episode (35 patients); and (3) those who were already hypertensive when they reached the recovery room (34 patients).

The studies performed could be subdivided into two parts. Part I describes the investigations performed during the development of hypertension whereas Part II describes the hemodynamic and humoral consequences of unilateral stellate block. Not all investigations were performed in all patients; numbers involved are delineated under each subsequent section.

Part I: Study of the Hypertensive Phase

Three sets of studies were performed: (1) hemodynamic evaluation, (2) determination of an index of baroreceptor sensitivity, and (3) sequential determination of plasma renin activity and plasma catecholamine levels.

Hemodynamic evaluation: Evaluation of hemodyamic characteristics of postcoronary bypass hypertension was performed in 44 patients. In an initial series of 17 patients, all patients studied had to be normotensive on arrival at the recovery room. Cardiac output (indocyanine green method) was measured in this normotensive phase; it was then repeated at the end of a 4 hour follow-up period if the patient remained normotensive (7 patients) or when hypertension had developed and blood pressure stabilized for at least 10 minutes (mean arterial pressure greater than 110 mm Hg) (10 patients). In a subsequent series of 27 patients, cardiac output was measured only during the hypertensive episode before the institution of therapy.

Baroreceptor studies: Seventeen patients had a baroreceptor sensitivity test as previously described by Bristow et al.[7] Of these 17 patients, 4 were normotensive after operation and remained so during the follow-up period, 8 were hypertensive on arrival at the recovery room and 5 were normotensive and then became hypertensive. The latter five patients were studied in the normotensive phase and then in the hypertensive phase, whereas the first two groups were studied only once. Because of the risks of pressure elevation, a modified method was adopted.[8] Intravenous nitroglycerin was used to decrease pressure; if an initial dose of 0.2 mg was not successful in reducing systolic pressure by at least 15 mm Hg, the test was repeated 3 to 5 minutes later using 0.4 mg. The correlation between each systolic pressure and the succeeding R-R interval was calculated; if significant ($P < 0.05$ at least), the slope of the regression line was taken as the index of baroreceptor sensitivity.[7] All beats, both inspiratory and expiratory, were included for calculation; however, premature beats and the following compensatory pause were excluded.

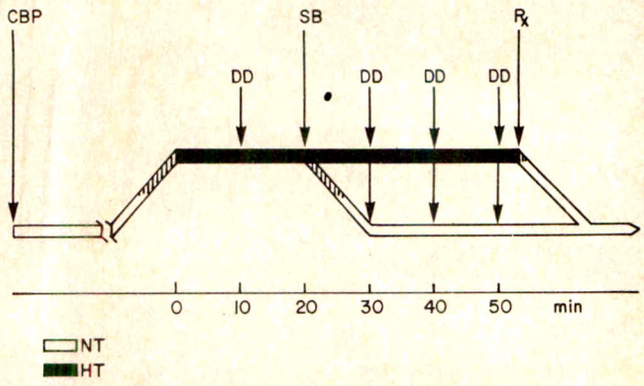

FIGURE 1. Protocol followed during hemodynamic evaluation of patients with postcoronary bypass (CBP) hypertension. DD = dye-dilution cardiac output determination; HT = hypertensive phase, NT = normotensive phase, R_x = intravenous nitroprusside infusion and SB = stellate block. In another series of patients, plasma renin activity and plasma catecholamine levels were obtained in the normotensive phase, when blood pressure started to increase and when it stabilized at hypertensive levels, and finally when hypertension was controlled by unilateral stellate block. (See text for details.)

Humoral Studies: Serial plasma renin activity and plasma catecholamine levels were obtained in 5 normotensive and 15 hypertensive patients. In the normotensive group, blood samples were first obtained 1/2 hour after arrival at the recovery room, and then 1 1/2 and 4 hours later. In the hypertensive group, samples were first obtained in the normotensive phase 30 minutes after arrival at the recovery room (mean aterial pressure less than 95 mm Hg) and then when mean arterial pressure began to increase with no obvious cause and finally before institution of treatment after the pressure stabilized at levels greater than 110 mm Hg.

Plasma renin activity was measured by radioimmunoassay of generated angiotensin I after an incubation period of 3 hours at pH 5.7.[9] *Plasma catecholamines* were measured by radioenzymatic assay.[10] Normal values for the laboratory averaged 1.2 ± 0.8 (standard deviation) ng/ml and 260 ± 120 (standard deviation) ng/liter, respectively.

Part II: Unilateral Stellate Block

Forty-five hypertensive patients were treated by unilateral stellate block. Either the right (30 patients) or left (15 patients) stellate ganglion was infiltrated with Xylocaine® (15 ml of a 2 percent solution) using a paratracheal approach at the level of Chassaignac's tubercle (C_6).[5] Choice of the side of infiltration was random and in the end, 30 patients had right stellate block and 15 had left stellate block. In no case were both ganglia infiltrated in the same patient. The effectiveness of the stellate block was determined by an increase in skin temperature of at least 5° F on the ipsilateral hand. If an effective stellate block failed to control blood pressure within 30 minutes, therapy with nitroprusside was instituted. During and after the stellate block, the patients were carefully monitored for signs of diminished cardiac performance.

Sequential cardiac output studies (27 patients) and sampling for plasma renin activity and plasma catecholamine levels (15 patients) were obtained before and after blockade (Fig. 1).

TABLE IV

Serial Changes in Plasma Catecholamine Levels After Coronary Bypass Surgery

	Normotensive Patients (no. = 5)			Hypertensive Patients (no. = 15)			
	C_1	C_2	C_3	C	HT_1	HT_2	RSB
Plasma catecholamines (ng/liter)							
Average	543 ±	870 ±	704 ±	710 ±	857 ±	838 ±	867 ±
SE	133	221	130	135	247	125	138

C_1, C_2 and C_3 represent, respectively, measurements of plasma catecholamines immediately after return to the recovery room, then 1 1/2 and 4 hours later in patients who remained normotensive throughout the follow-up period. In those who became hypertensive, plasma catecholamine levels were obtained in the normotensive phase (C = control), when blood pressure started to increase (HT_1), when blood pressure stabilized at the hypertensive level (HT_2), and finally when blood pressure normalized by unilateral (right) stellate block (RSB). Control values in the two groups (C_1 versus C) were not significantly different ($P > 0.3$).

in mean arterial pressure and the alteration in plasma catecholamine levels ($r = 0.50$, $P < 0.05$) (Fig. 3).

Part II: Unilateral Stellate Block

Hemodynamic effects: Effective stellate block was achieved in 45 patients as evidenced by a remarkable increase in the skin temperature of the ipsilateral forearm and hand (at least 5° F). In 36 (81 percent) of these patients, the unilateral block led to a rapid (within 5 to 10 minutes) reduction in blood pressure to normal or near normal levels. Subsequently, the blood pressure remained well controlled for the entire follow-up period in the coronary care unit. In no instance was a complication related to the stellate block itself; there was no significant increase in central venous pressure or left atrial pressure, and no disturbance in cardiac rate or rhythm was encountered even in those patients whose blood pressure was not decreased. There was no significant difference in the effectiveness of blood pressure control between block of the right or left stellate ganglion; arterial pressure was reduced in 24 of 30 patients after right stellate infiltration and in 12 of 15 patients with block of the left side (chi square analysis, not significant).

In 18 of the 27 patients who had cardiac output determination, the reduction in blood pressure in response to either right or left stellate block was associated with a significant diminution in total peripheral resistance whereas cardiac output did not change significantly (Table V). In all 45 patients, the stellate block resulted in some slowing of heart rate irrespective of the blood pressure response. The lack of an arterial pressure response to effective stellate block, either right or left, was not associated with significant changes in other hemodynamic indexes. In particular, there was no evidence of depressed cardiac performance in the patients studied. Central venous pressure was determined in all 45 patients whereas left atrial pressure was recorded in only 12 patients (15 of 30 with right stellate block and

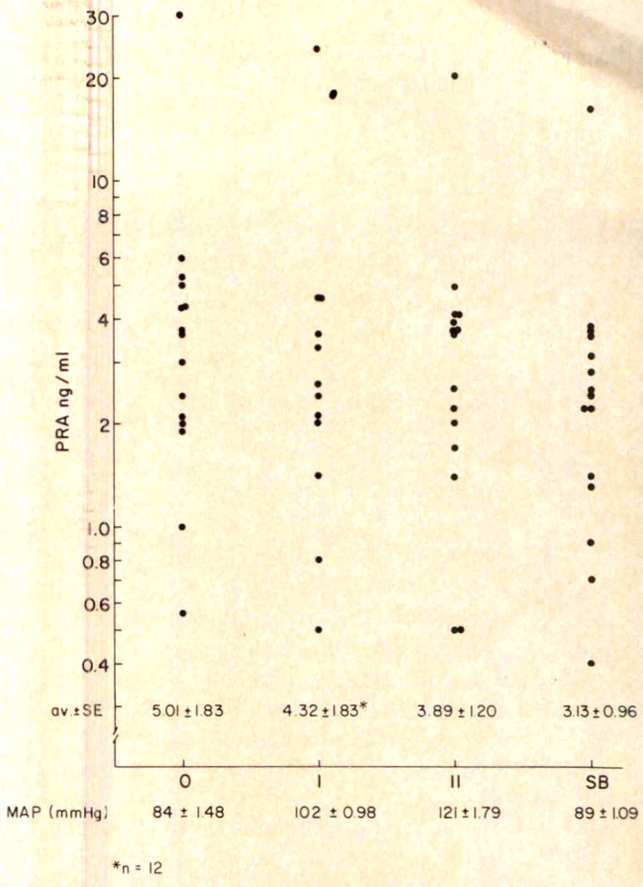

FIGURE 2. Sequential values of plasma renin activity (PRA) in 15 patients after coronary artery bypass. Measurements were obtained during the normotensive phase (0), when blood pressure started to increase (I, this phase included 12 patients only), when blood pressure stabilized at hypertensive levels (II) and when blood pressure was reduced to control or near control levels after right stellate block. Values reported are means ± standard error; variations of plasma renin activity at these different phases were not statistically significant. SB = stellate block.

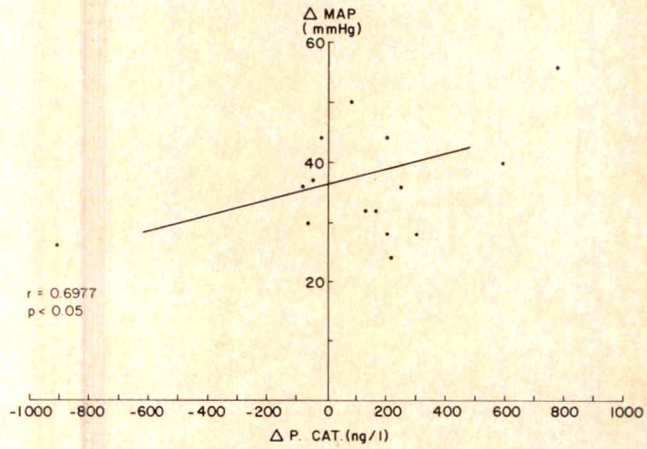

FIGURE 3. Correlation between the increase in mean arterial pressure (ΔMAP) and changes in plasma catecholamine levels (ΔP. CAT.) in the postcoronary bypass period in 15 patients in whom hypertension developed. Levels of plasma catecholamines used in this correlation were obtained when blood pressure stabilized at hypertensive levels. p = probability; r = correlation coefficient.

TABLE V

Control of Hypertension by Unilateral Stellate Block: Hemodynamic Response in 18 Patients (mean ± standard error of the mean)

	Right Stellate Block (no. = 9)			Left Stellate Block (no. = 9)		
	Before	After	P*	Before	After	P*
SBP	168 ± 5.5	119 ± 3.9	<0.001	185 ± 6.1	139 ± 6.4	<0.001
DBP	99 ± 2.8	75 ± 2.2	<0.001	98 ± 2.7	73 ± 2.9	<0.001
HR	94 ± 4.9	87 ± 5.1	<0.001	96 ± 5.8	88 ± 5.5	<0.01
CO	4.01 ± 0.4	3.49 ± 0.4	NS	4.12 ± 0.4	3.91 ± 0.4	NS
SI	22 ± 2.6	21 ± 2.8	NS	23 ± 2.4	24 ± 2.3	NS
TPR	66 ± 8.5	53 ± 6.4	<0.01	62 ± 4.1	49 ± 3.1	<0.025
CVP	9.2 ± 1.0	8.9 ± 1.1	NS	9.4 ± 1.3	9.6 ± 1.2	NS
LAP	14.5 ± 2.0	12.3 ± 2.6	NS	14.4 ± 1.4	14.2 ± 1.3	NS

* *P* (probability) value refers to statistical significance of paired *t* test.
Abbreviations are the same as in Table I.
CVP = central venous pressure (centimeters of saline solution); LAP = left atrial pressure (centimeters of saline solution).

8 of 15 with left stellate block); neither pressure was changed significantly by the stellate block (Table V).

Humoral effects: Changes in plasma renin activity and plasma catecholamine levels were monitored in 15 patients after right stellate block. There was no significant change in plasma renin activity with a reduction in blood pressure by the block in all 15 patients. As regards the plasma catecholamines, there was no significant change as far as group averages were concerned, but a significant correlation was found between the reduction in mean arterial pressure and changes in plasma catecholamines ($r = 0.53$, $P < 0.05$). However, the biologic significance of this correlation is difficult to assess because plasma catecholamine levels decreased in some patients (7 patients) and increased in others (8 patients), although the blood pressure was reduced in all.

Discussion

Hemodynamic Characteristics

Postcoronary bypass hypertension is now a well established entity.[1,2,4,12,13] It was observed in about 33 percent of patients undergoing myocardial revascularization surgery. Although elevation of blood pressure was described in the immediate postoperative period after other types of open heart surgery,[1,14] the incidence of this type of hypertension is much higher in association with coronary arterial surgery, either bypass graft or internal mammary artery implantation.[1] We[4] have previously shown by sequential hemodynamic determinations that this elevation of blood pressure was associated with an increase in total peripheral resistance, with no significant change in either output or heart rate. In addition, circumstantial evidence was presented against the attribution of this pressure increase to hypervolemia; it was shown that central venous and left atrial pressures were normal in these patients and did not increase with the development of hypertension.[4] Also, trials to reduce the volume of fluid infused to control the hypertension failed despite a decrease of central venous pressure by 1 or 2 cm of saline.[1,4]

Neurohumoral Factors

Role of renin-angiotensin system: The increase in total peripheral resistance pointed to a generalized mechanism for the increase in blood pressure. As to the reason for this increase, several possibilities could be suggested. Reports by Roberts et al.[13] emphasized the role of the renin-angiotensin system, because this system could be activated by cardiopulmonary bypass.[15] However, we have not found a particularly elevated plasma renin activity in patients in whom postcoronary bypass hypertension subsequently developed. There was no correlation on sequential determinations between the levels of mean arterial pressure and those of plasma renin activity, although plasma renin activity tended to show a decrease with the development of hypertension.

Role of reflex sympathetic overdrive: Sympathetic stimulation, however, was suggested by two observations, namely, the association of an elevated total peripheral resistance with persistent tachycardia and the presence of a significant correlation ($r = 0.50$, $P < 0.05$) between the increase in mean arterial pressure and elevations in plasma catecholamine levels (Fig. 3). Theoretically, such sympathetic overdrive could originate from different sources. In our experience, it could not be attributed to somatic stimuli such as cold or pain, because the patients were well sedated and resting. Blood gases were within normal limits. On the basis of the previous work of Peterson, Malliani, Brown, and their co-workers[16–19] the possibility of a sympathetic reflex originating from the heart, great vessels or coronary arteries was suggested. In favor of a reflex mechanism was the paroxysmal nature of this hypertension, its temporal relation to manipulation of the heart, coronary arteries and large vessels, and the absence of other obvious hemodynamic factors such as an increase in cardiac output or blood volume. More important was our success in controlling this hypertension in 81 percent of cases with unilateral stellate block.

Effects of stellate ganglion block: After either right or left stellate block, the hemodynamic changes asso-

ciated with normalization of blood pressure showed a decrease in total peripheral resistance with little or no change in cardiac output. Heart rate slowed in patients who did and did not respond to the stellate block. These results were interpreted to indicate that blood pressure control by stellate block was most probably due to interruption of afferent fibers coursing through or relaying in either stellate ganglion. If the block had acted mainly by interfering with efferent cardiac sympathetic drive, a depression of cardiac output would have been expected.[20] This is what happens with acute beta adrenergic blockade[21]; in such instances, cardiac output decreases but total peripheral resistance increases and blood pressure is left unchanged. The pattern is obviously quite different from the reduction in both arterial pressure and peripheral resistance by unilateral stellate block. Another argument pointing to the same conclusion could be derived from the equal reduction in heart rate caused by the stellate block in patients whose blood pressure was decreased by the stellate infiltration and in nonresponders (Table V). The decrease of blood pressure was therefore not dependent on this efferent effect of the block but resulted from a decrease in total peripheral resistance; this widespread effect of a unilateral block would suggest interruption of a pressor reflex. The paroxysmal nature of the hypertension appears to fit the description of positive feedback by Malliani et al.[19]

Baroreceptor sensitivity: Neurogenic factors could conceivably play another role in postcoronary bypass hypertension. The observation that heart rate did not slow when blood pressure increased might indicate a possible diminution in baroreceptor sensitivity, as happens in deafferentation hypertension. General anesthesia is known to suppress baroreceptor sensitivity.[22] This agrees with our findings of diminished baroreceptor sensitivity. However, this blunting of the reflex was observed in all patients, both those who remained normotensive and those who became hypertensive. There were only inconsistent changes in baroreceptor sensitivity in sequential determinations during the development of hypertension. It would seem, therefore, that this paroxysmal increase in blood pressure was not the result of reduced baroreceptor control. However, the reduction of baroreceptor sensitivity in this postoperative period might help set the stage for the development of hypertension from other causes.

Clinical Implications

Continued studies have confirmed that postcoronary bypass hypertension is related to an increase in total peripheral resistance that is possibly related to reflexes originating from the heart, great vessels or coronary arteries. This does not rule out the possibility that other factors might play a role under certain conditions. There could be many causes for an increase in blood pressure after coronary arterial surgery. A tentative classification differentiates between postoperative elevation of blood pressure with an obvious cause and postoperative hypertension occurring without an obvious cause, as well as between blood pressure elevation occurring early after operation and that developing weeks or months later. It is important, therefore, to define accurately the type of hypertension investigated. All patients reported on in this study were normotensive before operation; thus, discontinuance of antihypertensive therapy was not a factor in the postmyocardial revascularization hypertension. It is quite possible, however, that a rebound increase in blood pressure could occur in hypertensive patients whose antihypertensive medications are discontinued immediately before operation. Hypervolemia or a renal insult can play a significant role under other conditions. Only when these obvious and remediable causes are excluded is a consideration of reflexes and stellate block advisable. Careful administration of nitroprusside was effective when most other measures failed.

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Cardiac Receptors: Normal and Disturbed Function

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Widely distributed throughout the heart is a network of fibers connected to the medullary cardiovascular centers by nonmedullated vagal afferent fibers. When the traffic in these fibers is interrupted by vagal cooling, and the input from the arterial baroreceptors is prevented, the arterial blood pressure increases. Thus, these receptors act to inhibit tonically the vasomotor center. The receptors in the atria alter their rate of discharge with changes in atrial transmural pressure and contractility and are most active during end-inspiration and early expiration when the transmural pressure is maximal. The receptors in the ventricles respond to changes in ventricular end-diastolic pressure (preload), to the pressure generated during systole (afterload) and to changes in ventricular contractility. The cardiac mechanoreceptors have an equal or greater effect on the renal bed than the arterial mechanoreceptors and this effect is enhanced by hypercapnia. In animals, the cardiac mechanoreceptors have less control of the muscle vessels than the arterial mechanoreceptors, but the reverse is true in man. Both the cardiac and arterial mechanoreceptors can modulate the output of renin from the kidney, but the cardiac mechanoreceptors are more sensitive to small changes in blood volume. During coronary occlusion, in association with the bulging of the ischemic myocardium, the rate of discharge of these cardiac receptors is greatly increased.

The heart contains numerous mechanoreceptors that are activated by systolic and diastolic events. These receptors, like those of the carotid sinus and aortic arch, are capable of modulating the arterial blood pressure through reflex adjustments of heart rate and contractility and of the caliber of the systemic blood vessels.

The Cardiac Receptors

The cardiac receptors can be classified into three groups depending on the characteristics of their afferent connections to the central nervous system.

1. Large unencapsulated endings, localized mainly in the atria and venous-atrial junctions and subserved by medullated vagal afferents that conduct at velocities of 8 to 32 m/sec, are spontaneously active and discharge with cardiac rhythmicity at an average frequency of 18 impulses/sec. These receptors are strategically located so that one group signals atrial contraction and the other atrial filling. Details of their characteristics and function are provided in this Symposium by Linden.[1]

2. A network of fine terminal fibers distributed throughout the septal and free walls of the heart and subserved by nonmedullated vagal afferents that conduct at velocities of 2.5 m/sec or less (C-fibers) constitute 75 percent of the afferent cardiovagal fibers in the cat.[2] There is much conjecture as to the role of these receptors in normal circumstances and during malfunction of the cardiovascular system; this report will summarize current views.

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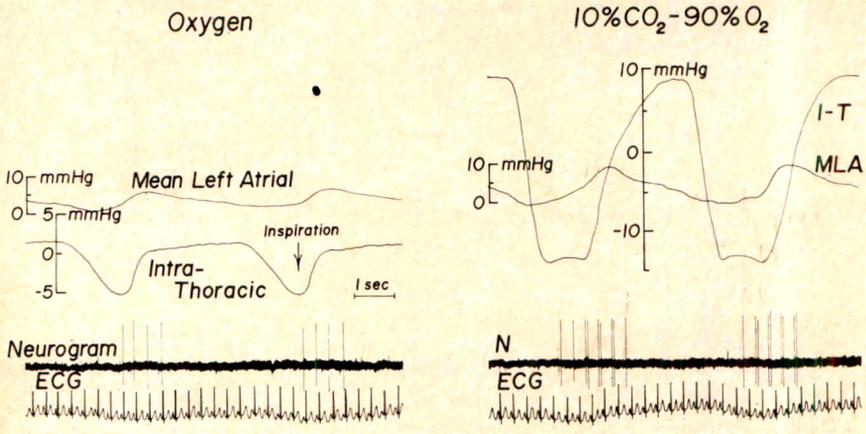

FIGURE 1. Discharge of left atrial receptors with nonmedullated vagal afferents in the spontaneously breathing cat. From above down are shown mean left atrial (MLA) pressure, intrathoracic (I-T) pressure (esophageal catheter positioned at heart level), neurogram (N) and electrocardiogram (ECG). **Left panel,** during quiet breathing of oxygen the receptor discharges regularly during end-inspiration and early expiration at the time the atrial transmural pressure is greatest. **Right panel,** when respiration was augmented by breathing 10 percent carbon dioxide, there was a marked increase in the frequency of discharge due to the large decrease in intrathoracic pressure that accompanied each breath. ECG = electrocardiogram. (Reprinted from Thames et al.[4] by permission of the American Heart Association, Inc.)

3. Receptors with medullated and nonmedullated fibers coursing to the spinal cord and medulla in the cardiac sympathetic nerves are widely distributed in the heart and great vessels. By contrast to the vagal afferents, these have a greater proportion of medullated to nonmedullated fibers. Their characteristics are reviewed elsewhere in this Symposium.

Atrial Receptors With Nonmedullated Vagal Afferents

Under resting conditions these receptors are silent or have a sparse irregular discharge of less than 1 impulse/sec. When excited above threshold levels, they discharge with cardiac rhythmicity and mainly during the *V* wave of the atrial pressure pulse. The threshold for those in the right atrium is 2 to 3 mm Hg (mean pressure), and those in left atrium 5 to 12 mm Hg. These receptors also discharge with cardiac rhythmicity during end-inspiration and early expiration when, in closed chest animals, the atrial transmural pressure is greatest (Fig. 1). Thus, these receptors respond to physiologic changes in atrial volume.[3,4]

Ventricular Receptors With Nonmedullated Vagal Afferents

Although these receptors are usually activated during ventricular systole, an increase in receptor discharge appears related to an increase in end-diastolic pressure (Fig. 2). Because ventricular systole is necessary for the increase in left ventricular end-diastolic pressure to increase receptor discharge, and because agents that increase cardiac contractility also increase the discharge rate, the relation of left ventricular end-diastolic pressure to frequency of discharge can be explained as the contribution of preload to the force developed in the subsequent systole.[5] In dogs surgically prepared so that only the atria, the ventricles or the lungs were the source of inhibitory traffic to the central nervous system, vagal block by cooling caused an increase in arterial blood pressure, thus demonstrating a tonic inhibition of the vasomotor center by cardiopulmonary receptors[6] (Fig. 3). Because vagal cooling interrupts the traffic in both medullated and nonmedullated fibers, experiments were conducted to see which of these fibers were responsible for this tonic vasomotor inhibition. In cats, electric excitation of the right cardiac nerve that stimulated only medullated fibers caused slight increases in heart rate and blood pressure. When the variables of stimulation were adjusted to excite the nonmedullated fibers, there was arterial hypotension, decreased renovascular resistance and bradycardia.[7] Selective vagal block by cooling in rabbits[8] and anodal block of the same nerve in cats[9] demonstrated that the tonic inhibition of the vasomotor center could be ascribed to inhibition of neural activity in nonmedullated fibers. The ubiquitous distribution of cardiopulmonary receptors throughout the heart and lungs allows them to respond to changes in preload, afterload, ventricular contractility and ventilation. They are thus in a unique position to be influenced by and to modulate cardiorespiratory behavior.

Interaction between the carotid sinus and the cardiopulmonary baroreceptors: This was examined by carrying out vagal block by cooling at different carotid sinus pressures.[10] When the carotid baroreceptors were activated maximally, there was no vascular response to vagal block by cooling. As carotid baroreceptor inhibition was withdrawn, there was a progressive increase in the response to the vagal block which became maximal at sinus pressures of less than 100 mm Hg. Thus, the inhibitory influence of the cardiopulmonary receptors varies inversely with the carotid sinus baroreceptors. This is in keeping with the finding that the nonmedullated afferent cardiac vagal fibers project to the solitary tract nucleus of the brain stem which is coincident with the termination of the fibers from the carotid sinus and the cardioaortic receptors.[11]

Cardiopulmonary receptors, carotid baroreceptors and sympathetic outflow: A comparison was made of the effects of the cardiopulmonary receptors subserved by nonmedullated vagal afferent fibers and the carotid baroreceptors on the sympathetic adrenergic outflow to the different vascular beds. At high and at moderate levels of activation of both receptor systems, muscle vasomotor fibers are less engaged by cardiopulmonary than by carotid baroreceptors. At low levels

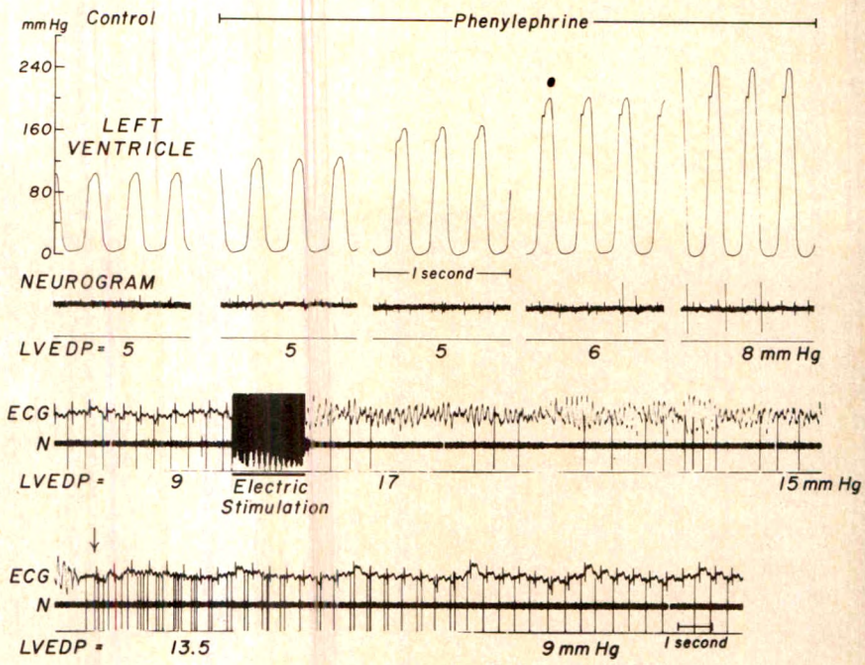

FIGURE 2. Activity in C-fiber vagal afferents from the left ventricle of cats. **Top panel,** effect of increase in left ventricular outflow resistance (infusion of phenylephrine) on discharge frequency. Note that left ventricular systolic pressure increased by 60 mm Hg without an increase in left ventricular end-diastolic pressure (LVEDP), during which the receptor remained silent. With the first increase in left ventricular diastolic pressure (6 mm Hg), the receptor discharged. **Lower panels,** effect of electrically induced fibrillation of ventricle on spontaneous activity of left ventricular afferent fiber. During fibrillation, activity decreases immediately, but after spontaneous defibrillation (**arrow**) traffic markedly increases before it returns to control. Increases in end-diastolic pressure are not accompanied by increases in receptor discharge until there is a coordinated ventricular contraction. ECG = electrocardiogram; N = neurogram. Data from Thames et al.[4] and Thorén.[26] (Reprinted by permission, from Donald and Shepherd.[5])

of activation, sympathetic outflow to muscle vessels appears to be equally influenced by both systems. The renal vasomotor fibers respond equally to high levels of activation of both reflex systems. At low levels of activation the renal vasomotor fibers appear to be more inhibited by the cardiopulmonary than by the carotid baroreceptors. This is ascribed to a greater engagement of the central neurons controlling renal than muscle vessels at low frequency of cardiac nerve stimulation.[12] Thus, the cardiopulmonary receptors buffer more effectively in the kidney than in muscle the reflex vasoconstriction produced by withdrawal of carotid baroreceptor activity. This still is so when the activity of the cardiopulmonary receptors is increased by hypervolemia.[5]

The differential engagement of the carotid and cardiopulmonary receptors with the central neuronal pools governing the sympathetic outflow to the periphery dictates the role of each system in counteracting various stresses. For example, during moderate hemorrhage the more powerful control of muscle resistance vessels by the carotid than by the cardiopulmonary baroreceptors is the reason the arterial blood pressure is better sustained by the carotid baroreceptors.[13]

It is possible to alter the relative control of different vascular beds mediated through arterial and cardiopulmonary baroreceptors. For example, hypercapnia in rabbits slightly augmented the increase in muscle resistance during vagal cold block but caused a fivefold potentiation of the block-induced increase in renal resistance. This phenomenon is not unique to the cardiopulmonary baroreflex; the aortic baroreflex is similarly influenced[14,15] (Fig. 4). That it might result from an interplay between the action of carbon dioxide on the central neurons controlling these vascular beds and afferent input from the receptors is speculated. Whatever the mechanism, it permits renal blood flow to be preserved during hypercapnia. This would have obvious benefits in contributing to the restoration of acid-base balance in respiratory acidosis.

Cardiopulmonary and arterial baroreceptors in human beings: The situation in human beings appears to be different in that the cardiopulmonary receptors have a much greater influence on muscle flow than do

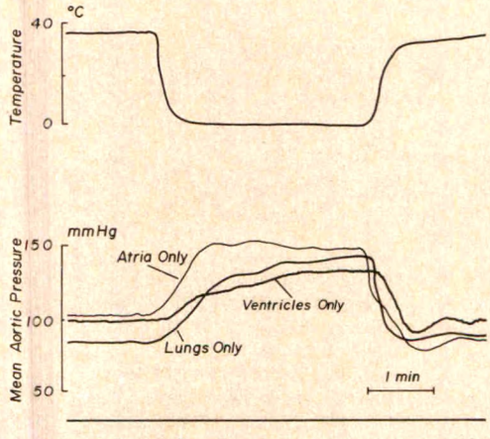

FIGURE 3. Demonstration that the atria, the ventricles and the lungs each exert a tonic influence on the cardiovascular centers. In one study, the lungs and ventricles were removed, leaving the beating atria only. In another, the lungs were removed and the atria denervated, leaving the innervated beating ventricles only. In a third, the heart was removed, leaving the lungs only which were mechanically ventilated. When the traffic in the vagal afferents from the receptors in each of these structures is interrupted by vagal cooling (**top**), there is an increase in aortic blood pressure due to increased sympathetic outflow to the heart and systemic blood vessels. Data from Mancia and Donald.[6]

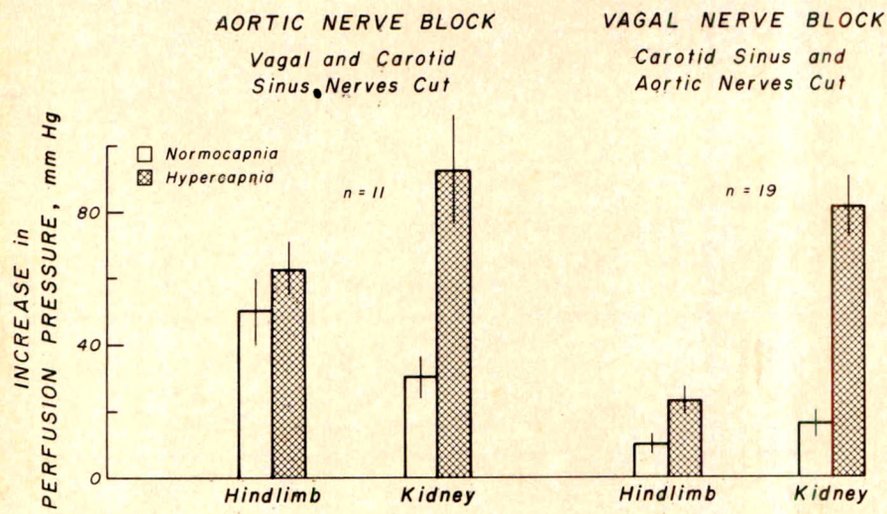

FIGURE 4. Effect of hypercapnia on the inhibition of hindlimb and renovascular resistance by aortic and cardiopulmonary mechanoreceptors in anesthetized rabbits. **Left panel,** vagal and carotid sinus nerves were cut before aortic nerve block by cooling. **Right panel,** carotid sinus and aortic nerves were cut before cold block of cervical vagal nerves. Note the greater augmentation by hypercapnia of the inhibitory influence of both systems on renal but not on hindlimb vascular resistance n = number of experiments. Redrawn from Ott and Shepherd.[14] (Reprinted by permission, from Donald and Shepherd.[5])

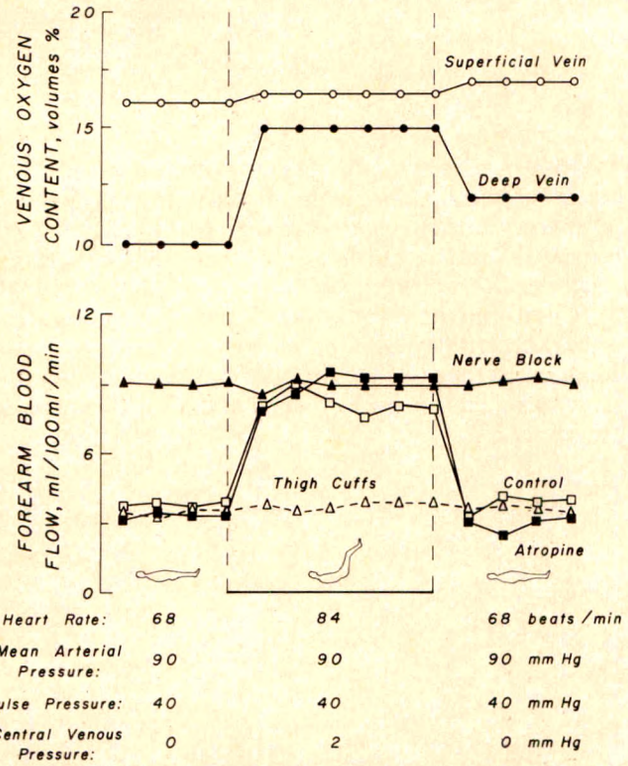

FIGURE 5. Effect on passive elevation of the legs of a normal subject on the circulation through the forearm. With leg elevation the blood flow in the forearm increases. This is due to an increase in muscle blood flow, since the oxygen content of the blood draining the forearm muscles increases (deep vein) but that of the blood draining the forearm skin (superficial vein) does not. The increased flow is due to reflex dilatation since it was prevented by blocking the sympathetic nerves to the forearm vessels with a local anesthetic. The dilatation was not affected by atropine, indicating that it was caused by decreased activity of noradrenergic fibers and not to activation of cholinergic fibers. It was caused by displacement of blood from the legs since it was prevented by inflation of thigh cuffs to suprasystolic pressure before the leg elevation. Since arterial mean and pulse pressures were unchanged, and central venous pressure increased, the reflex dilatation is attributed to excitation of receptors somewhere in the heart and lungs. Data from Roddie and Shepherd[27] and Roddie et al.[28] (Reprinted by permission, from Donald and Shepherd.[5])

the arterial baroreceptors. For example, changing from the horizontal to the feet-up position can cause an increase in forearm blood flow without an increase in mean or pulse pressure at the carotid sinuses. This increase in forearm blood flow did not occur after inflation of thigh cuffs to suprasystolic pressure or after blockade of the sympathetic nerves to the blood vessels of the forearm. Thus, the decrease in vascular resistance was mediated reflexly, resulting from a translocation of blood to the thorax. Analysis of the oxygen content of venous blood draining skin and muscle showed that the response was confined to the muscle vessels. Failure of atropine to reduce vasodilatation demonstrated that sympathetic cholinergic vasodilator fibers were not involved[16] (Fig. 5).

Increasing and decreasing the effective pressure at the carotid sinus by application of subatmospheric pressure to the neck or by manual compression of the common carotid arteries cause the classic changes in arterial blood pressure and heart rate. Neck suction does not alter blood flow in the forearm but there is a significant increase in vascular resistance in the forearm.[17] However, the increase in systemic arterial pressure with bilateral carotid occlusion is not accompanied by significant changes in vascular resistance in the calf.[5] The role of the low pressure versus the high pressure mechanoreceptors in man is discussed in this Symposium by Abboud.[18]

Release of Renin

In anesthetized dogs small reductions in circulating blood volume do not decrease afferent nerve traffic from the arterial baroreceptors but do result in an increase in renin release which is due to decreased activity of vagally innervated cardiopulmonary receptors.[19] This implies that cardiopulmonary receptors are more sensitive detectors of small changes in circulating blood volume than are carotid baroreceptors. Failure to find changes in renin when both receptor systems respond

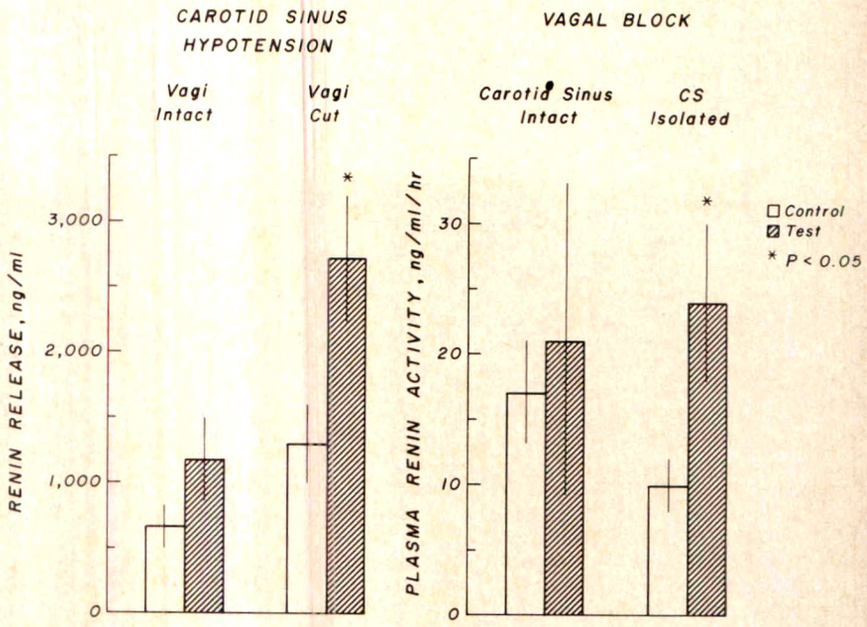

FIGURE 6. Interaction of carotid and cardiopulmonary mechanoreceptors in the release of renin. **Left panel,** effect of carotid sinus hypotension on the release of renin before and after vagotomy in anesthetized dogs with aortic nerves sectioned. Sinus hypotension is ineffective in increasing significantly the release of renin when the vagal nerves are intact. **Right panel,** effect of interruption of afferent vagal traffic from cardiopulmonary receptors with the carotid sinus (CS) intact and vascularly isolated in anesthetized dogs with aortic nerves sectioned. Vagal block is ineffective in increasing significantly the release of renin when the carotid baroreceptors are free to exert their buffering influence. Data from Jarecki et al.[29] (Reprinted by permission, from Donald and Shepherd.[5])

to a particular stress can be due to interaction between the systems (Fig. 6).

Involvement of Cardiopulmonary Afferents in Abnormal Circumstances

Obstruction to left ventricular outflow: The C-fiber vagal afferents and the sympathetic afferents from the left ventricle can be activated by increases in ventricular filling (preload) and in systemic arterial pressure (afterload). In anesthetized dogs acute obstruction to left ventricular outflow produces a reflex vasodilatation in skeletal muscle and skin. The vasodilatation is more marked in skeletal muscle and is blocked by vagotomy. Because obstruction to left ventricular inflow increased left atrial pressure but did not cause reflex vasodilatation, it was concluded that the vascular response was due to activation of left ventricular baroreceptors. Patients with aortic stenosis are prone to syncope on exertion. When they undertake supine exercise, the usual reflex constriction of the forearm vessels is inhibited or reversed. This has been attributed to activation of left ventricular receptors.[20]

Digitalis therapy: Small doses of acetylstrophanthidin applied to the epicardium of the left ventricle of dogs cause hypotension and bradycardia as a result of activation of receptors subserved by C-fibers.[21] This finding suggests that the bradycardia resulting from digitalis therapy in man may be caused in part at least by excitation of vagally innervated left ventricular receptors.

Coronary occlusion: Reduction in coronary blood flow in cats and dogs activates cardiac receptors with vagal and sympathetic medullated and nonmedullated fibers. In the cat left ventricular receptors with nonmedullated vagal afferents situated in the region supplied by the occluded coronary artery increased their activity together with the systolic bulging of the ischemic myocardium, suggesting that excitation is mechanical rather than chemical.[22] Studies in dogs[23] suggest that these inhibitory cardiac receptors have a preferential distribution to the inferior wall of the left ventricle.

Coronary embolization versus hemorrhage: In conscious dogs in which similar reductions in cardiac output and systemic arterial pressure have been produced by coronary embolization and by hemorrhage, those with coronary embolization had a well maintained renal blood flow and urine production, with normal intrarenal distribution of blood flow and urine-concentrating capability.[24] These functions were reduced in the group subjected to hemorrhage. The mechanism of this different behavior is suggested by the observation that coronary embolization in dogs is accompanied by a decrease in the postganglionic nerve activity to the kidney. Vagal section caused an immediate increase in sympathetic nerve traffic.[25] It is hypothesized that the increased activity of cardiac receptors due to cardiac dilatation or systolic bulging of the ischemic myocardium after coronary occlusion acts to buffer the increase in sympathetic nerve activity consequent to arterial hypotension. This will be more effective in the kidney than in the muscle vascular beds because of the different involvement of cardiac and arterial baroreceptors in the central neuronal pools controlling sympathetic outflow to these two vascular beds. During hemorrhage the combined withdrawal of inhibition exerted by each receptor group results in a marked increase in renal sympathetic nerve traffic. Thus, the cardiovascular response to coronary occlusion represents a balance between the effects of a decrease in carotid sinus inhibition and an increase in the depressor influence of the cardiac receptors.

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Atrial Reflexes and Renal Function

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Distension of small balloons in the venous-atrial junctions results in an increase in heart rate, urinary flow and sodium excretion. Two types of atrial receptors are described: one type, histologically known, discharging into myelinated fibers, and a second type, discharging into nonmyelinated ("C") fibers. These responses are mediated by the myelinated fibers. Experiments have shown that simulation of receptors discharging into the large myelinated vagal fibers is responsible for a reflex increase in heart rate mediated only by sympathetic nerves and for an increase in urinary flow.

The efferent pathway of the diuretic response is shown to be nervous and hormonal. Stimulation of atrial receptors causes (1) a reduction of activity in nerves to the kidney, causing an increase in both urinary volume and sodium excretion, and (2) the release of a blood-borne agent, possibly diuretic, that increases urinary volume but does not affect sodium excretion.

Henry et al.[1] in 1956 showed that distending a balloon in the left atrium so as to block the mitral orifice and increase the left atrial pressure about 20 cm of water resulted in an increase in urinary flow. Because balloons so distended also caused a reduction in cardiac output and blood pressure, it was even more remarkable that diuresis resulted. There was a decrease in solute concentration and the diuresis was labeled a water diuresis with all its implications.

In Leeds we were examining the effect of stimulating atrial receptors and found that discrete stimulation of the receptors resulted in a reflex increase in heart rate with the afferent nerves in the vagi and the efferent only in the sympathetic nerves, but there was no concomitant positive inotropic response.[2,3] A discrete stimulus to left atrial receptors was obtained by tying off the left lung and inserting small balloons 2 to 3 mm long into each of the pulmonary veins so that the tips lay at the pulmonary venous-atrial junctions. From histologic and physiologic studies it was known that atrial receptors were to be found mainly at the venous-atrial junctions.[3] A perfusion system using a balloon enabled the right atrial receptors to be stimulated discretely; a small balloon inserted into each atrial appendage was also shown to stimulate atrial receptors.[3] Stimulation of right and left atrial receptors, using these techniques of discrete stimulation by distending small balloons with no obstruction to blood flow through the atria, no decrease in cardiac output and no increase in pressure in the atria, always resulted in an increase in urinary flow. Also, when the resulting diuresis was compared with that produced by the larger stimulus of obstructing the mitral orifice in the manner described by Henry et al.,[1] we concluded that there was no reason to believe that any receptors other than atrial receptors were responsible for the diuresis.[4]

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Afferent Limb of the Reflex Diuresis

We[4] also showed that the afferent limb of the reflex diuresis was in the vagi. The technique used was to block the transmission in branches of the vagal nerves that were known to carry the afferent nerve impulses involved in the reflex increase in heart rate.[5] Experiments were performed in eight dogs; after diuretic responses to atrial distension were determined, atrial receptors were then stimulated again with the vagi cooled or sectioned in the chest. In seven of the eight dogs the diuretic response was abolished or greatly reduced, a result similar to that obtained in investigations of the heart rate reflex.[3] It was concluded that the increase in urinary flow was caused by a reflex from the atrial receptors and that the afferent limb was in the vagi. In experiments in 20 more dogs the application of the cooling techniques always resulted in abolition of the increase in urinary flow.

C fibers *versus* sympathetic afferent fibers: However, there are three sets of afferent nerves that emanate from the atrium, two in the vagi and one in the sympathetic system.[8] There are receptors situated mainly at the atrial-venous junctions that are visible in the subendocardial tissue histologically and that discharge into fast-conducting myelinated fibers and were thought to be involved in the heart rate-urinary response reflex.[3,6] Recently, Thoren[7] observed atrial receptors discharging into very slow-conducting vagal nonmyelinated fibers ("C" fibers). The exact structure and location of the endings of these "C" and "sympathetic" afferent fibers have so far not been observed histologically.

Effect of graded cooling of vagi: To distinguish which fibers mediated the urinary response a series of experiments were completed in chloralose-anesthetized dogs in which large balloons were distended to block the mitral orifice and cause the diuresis.[8] An increase in urinary flow was induced in each of seven dogs with the vagi maintained at 36° ± 1° C (first control period); the experiment was then repeated with the vagi cooled to either 18° or 12° C, and then again with the temperature of the nerves at 36° ± 1° C (second control period). The response at 18° or 12° C was expressed as a percent of the average of the control responses; the mean response at 18° C was 70 percent (range 65 to 78 percent; no. = 3) of the control value and that at 12° C was 28 percent (range 8 to 49 percent; no. = 4). In eight dogs the effect of cooling the vagi on the increase in activity of atrial receptors produced by the distension of a balloon in the left atrium was studied and calculated as just described. In seven receptors (four dogs) that discharged into myelinated fibers (mean conduction velocity 17.6 m/sec) the mean response at 18° C was 68 percent (range 28 to 100 percent) of the control value and that at 12° C was 25 percent (range 6 to 42 percent). In four dogs, six receptors that discharged into nonmyelinated fibers (conduction velocity less than 2 m/sec) were examined. In five the responses were only slightly reduced by cooling the vagi to 12° C (mean response 95 percent, range 78 to 100 percent, of the control value) and in a sixth the response was reduced to 43 percent at 18° C and abolished at 17° C.

Thus, on graded cooling of the afferent fibers in the vagi, only the effects on the responses of the receptors that discharge into myelinated fibers were similar to the effect on the urinary response observed previously. The effect on the response of nonmyelinated fibers was not related; also, "sympathetic" afferent fibers were not involved.[8] From these findings it is concluded that the atrial receptors that discharge into myelinated fibers in the vagus are the most likely receptors to mediate the increase in urinary flow; these are the stretch-sensitive receptors that have been observed histologically in the subendocardial tissue.[3]

Efferent Limb of the Reflex Diuresis

Nervous Efferent Pathways

This reflex also has an efferent nervous limb to the kidney.[9] Nervous impulses in efferent sympathetic nerves to the heart (right ansa subclavia), to the kidney, to the spleen and in the abdominal sympathetic trunk below the origin of the renal artery were recorded in anesthetized dogs. Electric activity changed in response to stimulation of left atrial receptors (very small balloons at the junctions) only in the nerves to two areas; during stimulation of atrial receptors the activity in the nerves to the heart increased but that in the nerves to the kidney decreased; in other nerves there was no change. This response in the nerves to the kidney was not secondary to changes in heart rate and was also abolished by cooling the vagi. These nerves to the kidney probably cause changes in blood flow and thus contribute to the diuresis; some evidence for this statement has been provided by Mason and Ledsome.[10] Recently Prosnitz and DiBona[11] claimed that these efferent nerves affect renal tubular sodium reabsorption without changes in renal hemodynamics.[11]

Activity in efferent nerves to the kidney: Reflex inhibition of renal nerves has also been shown to be caused by the subendocardial atrial receptors discharging into myelinated fibers.[12] Activity in efferent nerves to the kidney was examined while cooling both vagi in a graded manner[12] as already described herein. In this series of experiments[12] small balloons were positioned in the left pulmonary venous-atrial junctions and the atrial appendage. Both cervical vagi were placed on cooling thermodes in pools of paraffin. Activity in efferent renal nerves was recorded along with the electrocardiogram and pressures in the femoral artery, left atrium and trachea. The reflex increase in heart rate was prevented by giving bretylium tosylate (10 mg/kg body weight) to block the sympathetic nerves. The atrial receptors were stimulated and the activity in the renal nerves was observed with the vagi warm (32° to 37°C), with the vagi cooled (12° or 18°C) and finally with the vagi warm again.

Twelve nerve preparations were examined in six dogs. Distension of the balloons with the vagi warm resulted in a mean decrease in renal nerve impulse frequency of 28 percent (range 10 to 80 percent). These responses were not significantly affected during cooling of the vagi to 18° C but were significantly reduced or abolished at 12° C (mean 6 percent, range 0 to 26 per-

cent, $P < 0.001$). This reduction in response was the same as that described under similar conditions in afferent myelinated fibers in the vagi; in contrast, the response in nonmyelinated fibers[13] during distension of small balloons was not materially influenced by cooling of the vagi.[13] In a second group of experiments, balloons were distended with the vagi at a temperature of 9° C; at this temperature all responses in myelinated fibers are blocked and most responses in nonmyelinated fibers are transmitted. In six dogs, 50 units were obtained; none showed a significant response.

From these results, we conclude that during stimulation of atrial receptors, the vagal fibers that are involved in reflex reduction in activity in renal efferent nerves are myelinated, and the nonmyelinated fibers are unlikely to be involved in this reflex. Thus, the atrial receptors are the pulmonary venous-atrial junctions discharging into myelinated fibers are responsible for the increase in urinary flow and the decrease in renal nerve activity.

Blood-Borne Agents

The efferent nerves, however, are not necessary for the increase in urinary flow. The increase in this flow has been obtained even in denervated kidneys and in isolated perfused kidneys. Stimulation of atrial receptors still resulted in an increase in urinary flow after complete blockade of efferent sympathetic nerves in anesthetized dogs brought about by the injection of bretylium tosylate (10 mg/kg) and propranolol (1 mg/kg), which completely blocked reflex of sympathetic responses. The reflex increase in urinary flow was also obtained in the presence of atropine. Thus, one limb of this diuretic reflex response involves a blood-borne agent.

Reflex inhibition of secretion of antidiuretic hormone: Gauer and Henry[15] postulated that activation of the atrial reflex causes the diuresis by means of a reflex inhibition of the secretion of antidiuretic hormone from the postpituitary gland; this conclusion was based on the time relations of the diuretic response to obstruction of the mitral valve. Ledsome et al.[16] suggested earlier that the antidiuretic hormone was not involved; in their experiments it was shown that the diuresis could still be obtained in the presence of large amounts of infused vasopressin. Later, Mason and Ledsome[17] observed that decreasing a large infusion rate of vasopressin to a smaller but still large infusion rate resulted in a diuresis similar to that observed by distension of the balloons of the left atrium. This and other experiments allowed the conclusion that even with large concentrations of antidiuretic hormone in the blood the diuresis could still be obtained.

Effect of atrial receptor stimulation after pituitary ablation: Still controversial is the claim that stimulation of atrial receptors causes a reflex inhibition of the secretion of antidiuretic hormone, and many studies have been cited to support this hypothesis. However, most methods used to evoke a response have not been specific to atrial receptors. The following methods have been used: negative pressure breathing, immersion of subjects, centrifugation of subjects, dialysis, infusions, methods causing mitral obstruction and, lastly, distension of balloons at the pulmonary veins and left atrial receptors.

All methods but the last either alter the composition of the blood or cause mechanical changes in the circulatory system with secondary reflex effects; hence, it cannot be argued that only the left atrial receptors are stimulated. Therefore, we[18] examined the effects of distending both the large balloon in the body of the left atrium (in the manner described by Henry et al.[1]) and of stimulating left atrial receptors with the small balloons, on urinary flow and on the level of antidiuretic activity in the plasma of the anesthetized dog. The diuresis caused by distension of either balloon was not accompanied by a reduction in antidiuretic activity of the plasma (although, in fact, on each occasion of distension there was a diuresis). This conclusion was supported by further experiments in which the posterior pituitary gland of anesthetized dogs was ablated and yet the diuretic response could still be obtained,[19] although no antidiuretic activity was detectable in the plasma after ablation of the gland. In dogs anesthetized with chloralose the posterior pituitary gland was destroyed by electric coagulation. At postmortem examination the pituitary gland was charred and was observed both macroscopically and microscopically to be destroyed and to contain no antidiuretic hormone. A diuresis was obtained in each dog during distension of the balloon in the left atrium; the reflex diureses obtained after pituitary ablation were not different from those obtained with the pituitary intact.

Role of a blood-borne diuretic agent: It was therefore concluded that the diuresis obtained by stimulation of atrial receptors is not caused by reduction of antidiuretic hormone in the blood of these anesthetized animals.[19] In that investigation also, the diuresis was obtained during distension of the balloon in the left atrium of dogs after renal denervation and the administration of bretylium tosylate, which blocks postganglionic sympathetic nerve fibers, thus providing further evidence in favor of a blood-borne agent mediating the diuresis, even when the postpituitary gland is ablated. Additional evidence was obtained in suitable models for study of antidiuretic activity, the water-loaded, ethanol-anesthetized diuretic rats; these were unaffected by plasma obtained from dogs during stimulation of atrial receptors. Because the diuresis in such dogs is not accompanied by a consistent reduction in antidiuretic activity in the plasma (as already discussed), it was concluded that the blood-borne agent causing the increase in urinary flow was unlikely to be an antidiuretic agent but was most likely to be a diuretic agent, as yet of unknown origin.

Atrial Receptors and Sodium Excretion

Denervated versus innervated kidney: In chloralose-anesthetized dogs large and small balloons to stimulate only the atrial receptors were again used to evoke urinary responses. The dogs were prepared with one kidney denervated and one innervated.[20] Interim results suggest that the large balloon (19 experiments) caused an increase in urinary flow in the innervated

kidney of 100 ± 19 percent (standard error of the mean) and in the denervated kidney of 87 ± 19 percent; the difference was statistically significant ($P < 0.01$). Sodium excretion increased by 74 ± 23 percent in the innervated and 44 ± 21 percent in the denervated kidney; although the change in the denervated kidney was not in itself significant, the difference between the responses of the two kidneys was significant ($P < 0.01$). Thus, the innervated kidney excreted more water and more sodium than the denervated kidney. In a separate group of 12 experiments the small balloons were used; there was less stimulus and the responses were smaller but similar, except now the denervated kidney increased its sodium excretion by 14 ± 6 percent and this increase was statistically significant ($P < 0.05$). This value was also less than that from the innervated kidney, which confirms the conclusion from the use of mitral obstruction that more sodium was excreted by the innervated kidney. Thus, in anesthetized dogs, stimulation of left atrial receptors results in a greater diuresis and natriuresis in the innervated kidney than in the denervated kidney in the same animal.

Humoral nature of the diuretic and natriuretic responses: The biologic significance of the small increase in sodium excretion resulting from the humoral agent (denervated kidney), however, is not clear because usually there are associated hemodynamic changes. An investigation[21] was therefore undertaken to examine the humoral nature of the diuretic and natriuretic responses to stimulation of atrial receptors; the heart and kidney were "pharmacologically denervated" and the blood pressure and heart rate remained constant throughout each experiment. In dogs anesthetized with chloralose the chest was opened on the left side and the following drugs were administered intravenously: bretylium tosylate, 10 mg/kg; atropine, 0.5 mg/kg and atenolol, 2.0 mg/kg. The left atrial receptors were stimulated by distending the small balloons located in the pulmonary venous-atrial junctions and the left atrial appendage. The balloons were distended 11 times in eight dogs; the left atrial pressure, femoral arterial pressure and heart rate during the test period did not change significantly when compared with the respective control values. The urinary flow increased significantly ($P < 0.001$; t test for paired data) from 0.5 ± 0.2 ml/min (mean ± standard deviation) during the control periods to 0.7 ± 0.3 ml/min during the test period. The urinary sodium concentration decreased significantly ($P < 0.005$; t test for paired data) from 133 ± 86 to 107 ± 84 millimolar/liter (mean ± SD) whereas sodium excretion did not change significantly ($P < 0.7$; t test for paired data) between the control (70 ± 65 μmolar/min) and test periods (73 ± 71 μmolar/min) (mean ± SD).

It can thus be concluded that distension of the pulmonary venous-atrial junctions and left atrial appendage without changes in left atrial pressure, arterial pressure and heart rate results in an increase in urinary flow but not in sodium excretion in pharmacologically denervated kidneys. It is concluded that the humoral agent responsible is only diuretic.

Nature of the humoral diuretic agent: Recently we have been trying to investigate this diuretic agent using the malpighian tubules of the South American blood-sucking bug Rhodnius prolixus.[22] Extracts of dog plasma obtained during the control periods and during distension of the balloon and thus during diuresis gave a different response when applied to the malpighian tubules, with the tubules suspended in liquid paraffin. This difference was abolished when plasma was obtained from the dog during distension of the balloons with the vagi sectioned or cooled, that is, with procedures that also abolished the diuretic response. This malpighian tubule preparation is being used during the continued extraction process in order to detect the presence or absence of the diuretic agent in the extracts. This agent is not antidiuretic hormone because the malpighian tubules are not affected by antidiuretic hormone and because incubation of the plasma with sodium thioglycollate, which destroys antidiuretic hormone, did not affect the action of extracts of the plasma obtained during the distension diuresis.

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Cardiac Reflexes in Normotensive and Spontaneously Hypertensive Rats

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Characteristics of left atrial receptors were studied in normotensive control (Wistar) and spontaneously hypertensive rats. The left atrial pressure was chronically elevated in spontaneously hypertensive rats and at the end of the expiratory phase was 10.3 mm Hg as compared with 4.6 mm Hg in normotensive control rats. The thresholds of the receptor endings were twice as high in the hypertensive as in the normotensive rats (10.2 and 4.6 mm Hg, respectively). In other experiments the reflex inhibition of renal sympathetic outflow was studied during plasma infusion in baroreceptor denervated normotensive and hypertensive rats and was inhibited at a lower left atrial pressure in the former. These differences are attributed to decreased distensibility of the left atrium in spontaneously hypertensive rats.

The reflex splanchnic nerve inhibition with volume load also was recorded in awake rats. At a 10 percent increase in blood volume, splanchnic outflow was more significantly decreased in spontaneously hypertensive than in normotensive rats. The mechanism underlying such a hyperreactive volume receptor response is unknown, but a less distensible venous system, centrally or peripherally, might be a contributing factor.

The role of cardiac reflexes in cardiovascular control has in recent years been the subject of a great number of studies.[1–5] There are two types of endings in the heart of dogs and cats. One type, connected to medullated axons, is located in the atrium at the venous-atrial junction.[3] The bursting discharge in these endings corresponds to atrial contraction (A type) or atrial filling (B type). When these endings are activated, there is reflex tachycardia and an increase in urinary flow.[3,5] There are also many receptors with nonmedullated vagal afferent fibers (C fibers) in the heart.[5–8] They seem to be located throughout the entire heart and respond mainly to changes in cardiac filling.[9,10] When activated, these receptors induce powerful depressor reflexes with marked reflex bradycardia and sympathetic inhibition especially in the kidney.[5]

Cardiopulmonary receptors inhibit the medullary vasomotor centers tonically because interruption of the afferent vagal traffic can induce pressor reflexes, especially if the buffering influences from the arterial baroreceptors are controlled.[5,11–13] There is also a tonic restraint in renin release from vagal afferent fibers[5,14] that is mediated by way of the C fibers.[5,15,16] Also found in man is evidence of a tonic vasomotor inhibition from low pressure receptors in the cardiopulmonary area. Thus, moderate degrees of lower body negative pressure can decrease central blood volume and cause vasocontriction in the skeletal muscle without any changes in blood pressure.[17]

The aim of this study is to describe how these cardiac receptors are reset during primary hypertension. The characteristics of cardiac endings in normotensive and spontaneously hypertensive rats were compared and the reflex effects of volume loading examined.

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Cardiac Receptors in Normotensive Rats

Left atrial receptors: There are no data on the characteristics of cardiac receptors with vagal afferent fibers in rats. A series of experiments were therefore performed on adult normotensive Wistar rats to examine the characteristics of these receptors.[18] A great number of left atrial receptors were examined, many of which behaved similarly to the medullated atrial B receptors in dogs and cats, discharging with a high frequency burst of activity with each cardiac cycle (Fig. 1C). Other receptors discharged with low frequency (Fig. 1, A and B), most often without any relation to the cardiac cycle (Fig. 1A). The peculiar finding was that all receptors examined had slowly conducting afferent C fibers. Suprisingly, no left ventricular receptors could be located.

High versus low frequency receptors: An attempt was made to analyze separately the characteristics of high and low frequency receptors. Arbitrarily, receptors with a maximal discharge frequency above 25 hertz were called high frequency receptors, and receptors whose discharge frequency was below 25 hertz were called low frequency receptors. The threshold for high frequency receptors was significantly lower than that for low frequency receptors. Furthermore, all high frequency receptors displayed an irregular firing pattern. Therefore, this arbitrary grouping of atrial C fibers might represent two functionally different types of receptors.

In preliminary experiments the characteristics of left atrial receptors in adult rats of the Wistar-Kyoto strain of normotensive rats (WKR) were studied. Three high frequency receptors had thresholds and pressure response curves within the range of normal Wistar rats.

Spontaneously Hypertensive Rats

Resetting of left atrial receptors in spontaneously hypertensive rats: The characteristics of left atrial receptors in adult spontaneously hypertensive rats were examined, and a high frequency bursting discharge pattern was found.[19] These receptor endings had higher thresholds than those in normotensive control rats. Mean left atrial pressure at threshold was 10.2 mm Hg in the hypertensive 4.6 mm Hg in the normotensive rats. The pressure response curves were also significantly displaced to the right in the spontaneously hypertensive rat (Fig. 2). Thus, these receptor endings operate at a higher pressure level in spontaneously hypertensive rats, but there is no difference in maximal discharge frequencies between the two strains of rats.

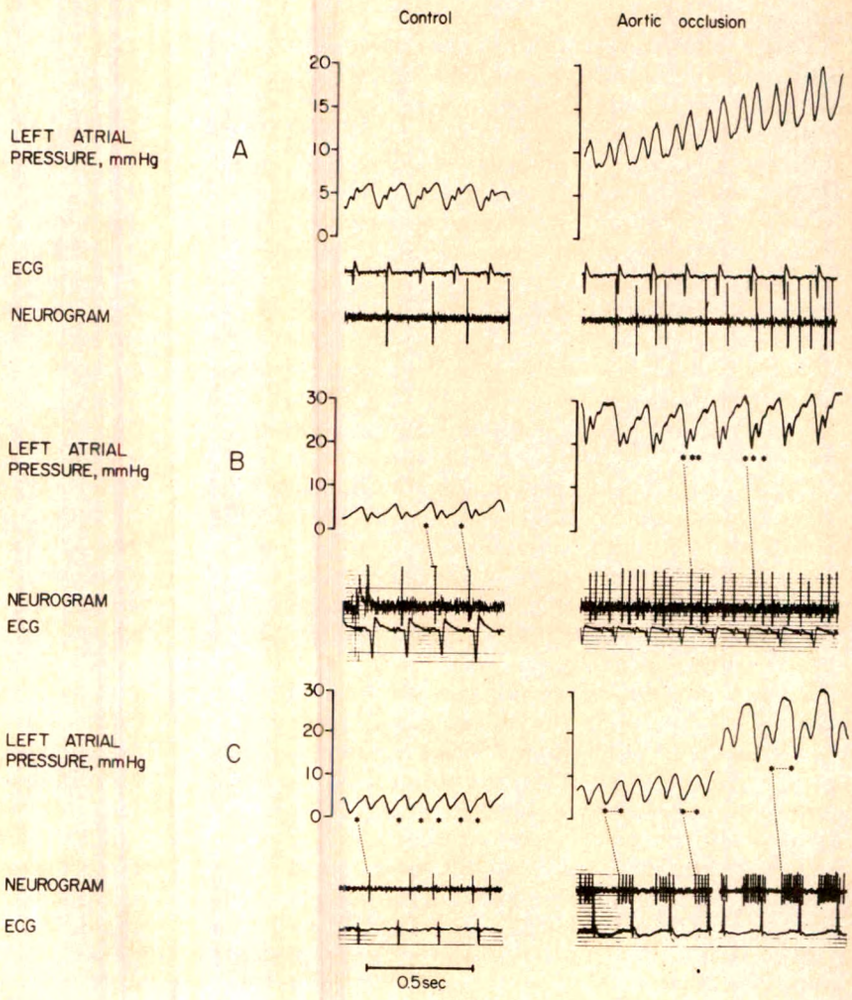

FIGURE 1. Left atrial pressure, electrocardiogram (ECG) and activity in three left atrial C fiber endings in three rats. The receptor in **panel A** has a low frequent irregular discharge on activation and is included with the low frequency receptors. The receptor in the neurogram in **panel B** is a low frequency receptor showing cardiac rhythmicity on elevation of left atrial pressure. The receptor in **panel C** is in the control situation, activated alternatively in the *a* and *v* wave, but on elevation of left atrial pressure the receptor shows a progressive discharge in relation to the *v* wave. (The **asterisks** indicate the corrected position in the cardiac cycle of the receptor activation). (Reproduced from Thoren et al.[18] by permission.)

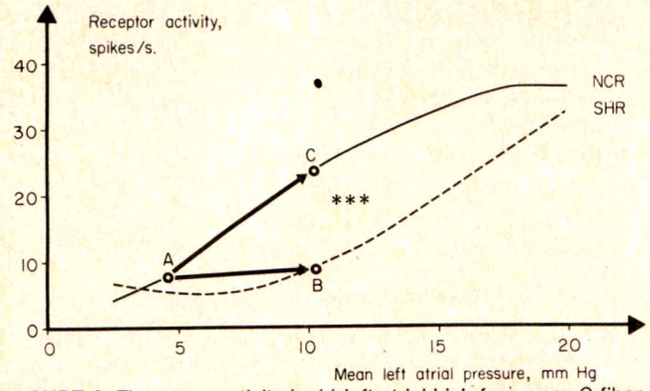

FIGURE 2. The mean activity in 11 left atrial high frequency C fiber endings in a spontaneously hypertensive rat (SHR) and similar data from 8 high frequency receptors in a normotensive control rat (NCR). Also shown is the mean left atrial pressure at end expiration in the normotensive (A) and the hypertensive (B, C) rat. Because of the resetting of the receptors there is no clear change in receptor activity in the hypertensive rat (B) despite an increase in left atrial pressure. C indicates the estimated receptor activity in the hypertensive rat in the absence of receptor resetting.

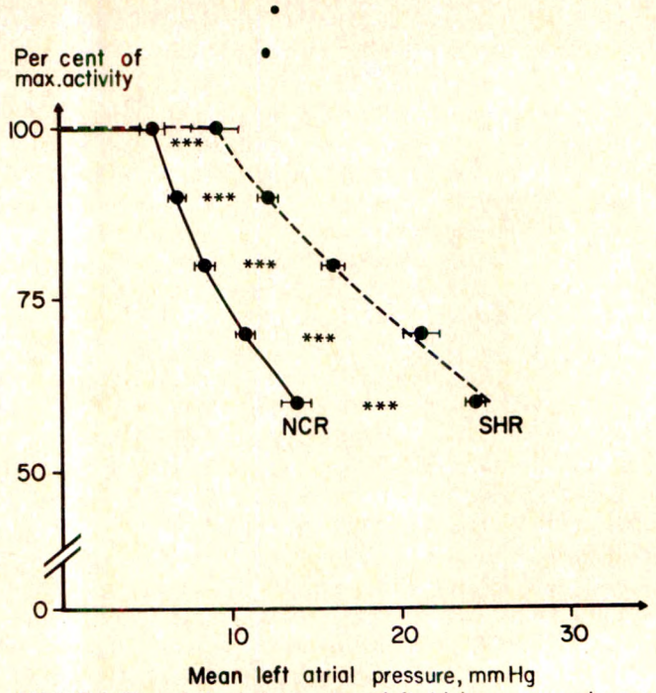

FIGURE 3. The relation between mean left atrial pressure and mean rectified renal nervous activity in six normotensive control (NCR) and six spontaneously hypertensive rats (SHR) during volume loading with horse plasma. The changes in renal activity are expressed as a percent of maximal (max.) control activity. (*** = $P < 0.001$). (Reproduced from Ricksten et al.,[21] by permission.)

No receptors with low frequency discharge were found in spontaneously hypertensive rats. Perhaps, their threshold values were too high to be found with the technique used.

Left atrial pressure in normotensive and spontaneously hypertensive rats: The left atrial pressure was measured in adult rats of the two strains.[20] Thin catheters were placed in the left atrium by means of a small thoracotomy. The animals were allowed to recover about 1 week, and the left atrial pressure was measured when the animals were awake. The mean pressure at the end of the expiratory phase was twice as high in spontaneously hypertensive as in normotensive rats (10.3 and 4.6 mm Hg, respectively). Thus, although the atrial receptors in spontaneously hypertensive rats have a higher threshold, this resetting is offset by an increased left atrial pressure.

The obvious question is whether the atrial receptor activity at rest is higher or lower in spontaneously hypertensive rats in comparison with normotensive rats. No conclusion can be drawn at this point because the threshold for receptor activation seems to be reset to about the same extent as the left atrial pressure, so that the receptor discharge in spontaneously hypertensive rats is not significantly different from that in normotensive control rats (Fig. 2).

Reflex control of renal sympathetic outflow during volume load: The reflex inhibition of sympathetic outflow to the kidney during volume load was measured in adult anesthetized normotensive control and spontaneously hypertensive rats.[21] The arterial baroreceptors were denervated. The observed renal nerve inhibition was mediated by the vagal nerves and was due to activation of receptors in the left side of the heart, presumably the left atrial endings. The relation between renal nerve inhibition and left atrial pressure is shown in Figure 3 during volume loading with horse plasma. The sympathetic outflow was inhibited at lower left atrial pressure in normotensive control than in spontaneously hypertensive rats, and the difference in the left atrial pressure threshold for reflex inhibition was similar to the difference in threshold for afferent traffic from the receptors (Fig. 2).

In this study the left atrial pressure increased much more on graded plasma transfusion in spontaneously hypertensive than in normotensive control rats. Thus, infusion of 1 ml of plasma/100 g of body weight increased left atrial pressure 2 mm Hg in normotensive control rats and 8 mm Hg in spontaneously hypertensive rats. This difference may reflect vessels with less distensible capacitance, centrally or peripherally, in spontaneously hypertensive rats compared with normotensive control rats.

Control of splanchnic nerve traffic in awake rats: Splanchnic nerve traffic in awake rats has been recorded.[22] With the rat under brief pentobarbital sodium anesthesia biopolar electrodes were placed on the left splanchnic nerve and isolated with silicone rubber (Wacker, Sil Gel 604). The animals were allowed to recover 1 or 2 days, and the nerve activity was then studied during volume expansion with blood obtained from rats in the same colonies.

The relation between changes in blood volume was plotted against the percent inhibition of splanchnic nerve traffic. At 10 percent blood volume expansion, spontaneously hypertensive rats showed a significantly more pronounced inhibition (43 percent) in comparison with normotensive control rats (33 percent). This in-

creased response was not due to an augmented arterial baroreceptor reflex because arterial blood pressure was increased less in the hypertensive rats and the sensitivity of the arterial baroreceptor reflex tended to be lower. The most likely explanation is an augmented low pressure receptor response in spontaneously hypertensive rats. This might seem like a paradox because, as discussed earlier (Fig. 2), the left atrial receptors are reset in spontaneously hypertensive rats to a higher threshold and a lower sensitivity. However, the resetting of the receptors might be offset by an altered distensibility of the capacitance system. A graded change in blood volume would increase left atrial pressure much more in spontaneously hypertensive rats, so that a more marked atrial receptor activation would occur despite the presence of receptor resetting. However, this hypothesis can only be confirmed after more experimental work.

Functional Aspects of Atrial Receptor Resetting

Cardiopulmonary reflexes are likely to be important in tonic vasomotor control of the circulation and in blood volume regulation because of their marked effects on the renal sympathetic outflow. Changes in renal sympathetic outflow can also influence sodium excretion[23] and renin release.[24] Renin release in spontaneously hypertensive rats is inhibited, most likely because of an increased load on cardiac receptors.[25] This depression seemed more pronounced in younger (5 weeks) than in older animals with established hypertension despite the significant increase in left atrial pressure in the older animals. A possible reason might be the resetting of the cardiac C fibers in established hypertension.

The resetting of the left atrial C fibers in the hypertensive animal is of interest in another respect. Such animals show significant hypertrophy of the left ventricle with a secondary shift of the Frank-Starling curve to the right, indicating that the hypertensive heart needs a considerably higher filling pressure to maintain an adequate stroke volume.[26] Therefore, it is important in spontaneously hypertensive rats that the left atrial receptors be reset to maintain the filling pressure of the left ventricle; otherwise, the stroke volume would decrease. Atrial receptors are reset during experimental heart failure in dogs.[27,28] These atrial receptors are very insensitive to pressure changes and their maximal discharge rate is clearly subnormal.[27] One likely mechanism is degeneration of the receptor ending.[28] In contrast, the maximal atrial receptor discharge is normal in spontaneously hypertensive rats, and there is no evidence that their cardiac hypertrophy is of a degenerative nature.[26] Instead, the resetting of the receptors is likely due to a structural adaptation of the left atrial wall. Thus, atrial receptor resetting in spontaneously hypertensive rats is not a good model of atrial receptor resetting in animals with heart failure. In spontaneously hypertensive rats the receptors are reset to a higher threshold, but from this new left atrial pressure level, changes in blood volume induce even more marked changes in receptor activity and reflex nerve inhibition.

Another interesting phenomenon in hypertensive animals and man is the exaggerated natriuretic response to saline loading.[29] This response may be due in part to an exaggerated nerve inhibition in the spontaneously hypertensive rat on the volume load, because the renal nerves are known to influence significantly both sodium excretion[23] and renin release.[24]

Resetting of Cardiac Receptors in Hypertensive Man

Does resetting the cardiac receptors in established hypertension in rats have any significance in the pathophysiologic aspects of essential hypertension in man? Patients with mild essential hypertension and low renin values have a 30 percent increase in central blood volume with no change in total blood volume.[29,30] The increased central blood volume might activate the cardiac receptors and reflexly inhibit renin release. In contrast, patients with mild high renin essential (borderline) hypertension have an increased sympathetic outflow to the peripheral vessels but no centralization of the blood volume.[31] Patients with established hypertension that is more severe do not have this reverse relation between the central blood volume and the renin level,[32] possibly because of resetting of the cardiac receptors.

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Reflex Control of the Heart

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The control of heart rate by the arterial baroreceptors and the evidence that these reflexes are impaired in people with raised arterial pressure are reviewed. The results with the Oxford phenylephrine test are compared with those using neck cuff methods as the stimulus. It is concluded that the neck cuff method gives useful information about heart rate changes but is less reliable when blood pressure is used as the response, because the relatively slow changes in arterial smooth muscle tone are probably the result of the differing information sensed by the carotid and aortic receptors. Contrary to the diminution in baroreflex gain seen with the phenylephrine methods, Mancia and his colleagues in Milan (using a neck cuff) report increased response of blood pressure in patients with hypertension. This may be a result of the increased arteriolar smooth muscle in hypertension. The evidence for the existence of neurogenic "deafferentation" hypertension is reviewed; it is concluded that denervation hypertension does exist, despite the experiments of Cowley and Guyton. It is possible that some cases of human essential hypertension may be the result of arterial baroreceptor partial denervation caused by stiffening of the baroreceptor areas by arteriosclerosis.

This study will review the reflex control of the heart, and particularly heart rate, with regard to changes that occur in association with elevated blood pressure. Although there are some reservations and uncertainties, evidence that baroreflex control of the heart is impaired in hypertension is increasing. I will discuss whether this impaired function is important in the genesis and maintenance of hypertension in man.

Speculation that dysfunction of the carotid baroreflex might cause hypertension soon followed the discovery of the powerful effects of the carotid sinus on blood pressure and heart rate.[1] However, experiments using denervation of the carotid and aortic baroreceptor areas in animals did not mimic human hypertension in that the blood pressure appeared to be very labile, to decrease to normal levels during sleep and to be accompanied by excessive tachycardia. For these reasons support for the neurogenic origin of human hypertension began to wane. A further blow was dealt by the experiments of Cowley and his colleagues[2] in Guyton's laboratory. They showed that when the baroreceptors of dogs were denervated and the dogs kept under quiet isolated conditions, the average blood pressure over 24 hours was slightly elevated, although it was much more variable than usual. These experiments have been criticized on several counts. First, there is no doubt that sustained hypertension can be produced in several other species by baroreceptor denervation. Second, others[3] have been able to produce hypertension in dogs by more complete baroreceptor denervation. Third, the conditions of isolation were artificial and if the animals had been subject to normal confrontation, their pressures would have been higher. It is true that the pressures decrease during sleep, but the same is true in human hypertension.[4]

Methods of Quantifying Reflex Gain Using Drugs

Our group in Oxford has been concerned with the reflex control of arterial pressure in man and we devised a method of quantitating this.

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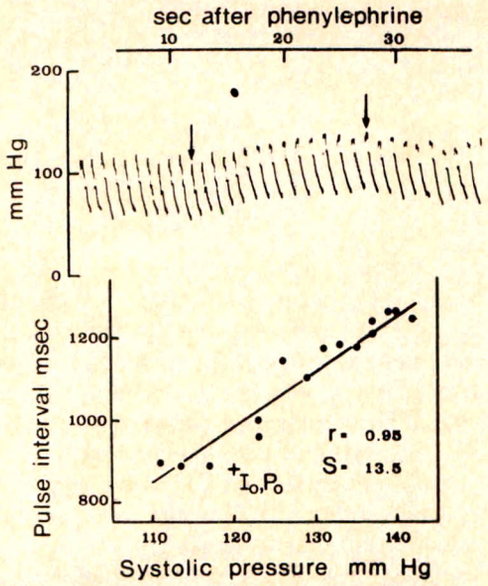

FIGURE 1. Phenylephrine method of baroreflex quantitation. A bolus of phenylephrine of 50 to 150 μg has been injected intravenously some seconds before and causes the increase in brachial arterial pressure (**top**). Between the **arrows** the successive values of pulse interval are regressed on the immediately preceding systolic pressure values to give the linear plot seen below. The slope of the line, in this man 13.5 msec/mm Hg, gives a measure of the gain of the reflex arc for heart rate control. $^{+}$ I_o, P_o = average for control pulse interval (I_o) and control pulse pressure (P_o) before phenylephrine. (Reprinted by permission, from Bristow et al.[23])

Originally the method was used to examine the reflex control of pressure during sleep.[5]

Figure 1 shows the principle. A small dose of a pressor agent such as phenylephrine is injected intravenously and, as the pressure increases, the heart rate slows reflexly. If during the 20 to 30 mm Hg pressure increase we plot the systolic pressure of a beat against the following pulse interval, we obtain a linear plot. The slope of this line (msec increase in pulse interval for 1 mm increase in systolic pressure) gives a measure of reflex sensitivity. When we examined the resting supine reflex sensitivity of a large number of untreated subjects, we found a striking linear decrease in sensitivity with increasing age and independently with increasing resting arterial pressure.[6]

Figure 2 shows an updated version of this plot and includes 114 subjects. In all age cohorts those with the higher pressures show poorer baroreflex control of heart rate. This finding was confirmed by Korner et al.[7] using the "steady state" method in which the pressor agent or trinitrin is infused over 15 to 20 sec to reach a plateau or trough of blood pressure. The advantages of this method are that it includes sympathetic as well as vagal responses and that the responses to increasing and decreasing pressures fall on the same slope. However, the method is relatively insensitive. Korner et al. found that the reflex responses in hypertensive subjects were about 60 percent of those in patients with normal pressures. We found an 8- to 10-fold range over the extremes of sensitivity (Fig. 2). Others[8] found that patients with borderline hypertension also had reduced reflex sensitivity. It should be noted from Figure 2, however, that the terms hypertension and normotension are arbitrary divisions and that the changes in reflex sensitivity represent a continuum, in parallel with the continuous distribution of blood pressure in the population.[9]

The baroreceptor endings are in juxtaposition to smooth muscle cells at the junction of the adventitia and the outer layers of the muscular media.[10] The methods that use vasoactive drugs are therefore open to the objection that they might not only change arterial pressure but also influence the receptor mechanism

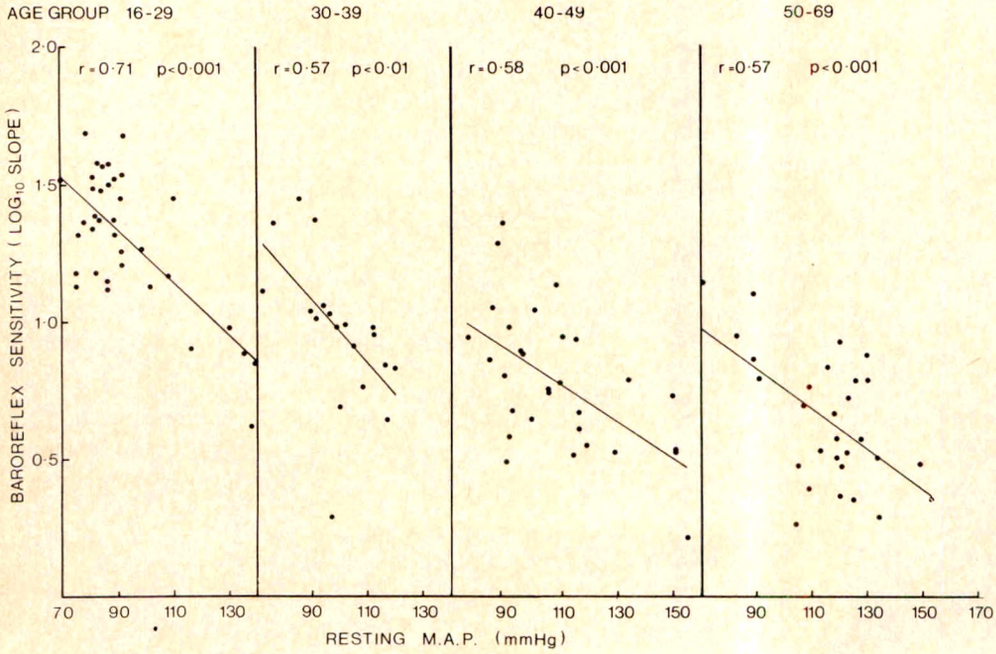

FIGURE 2. Log of slope (gain) of averaged phenylephrine baroreflex tests in 114 subjects arranged by age and resting mean arterial pressure (M.A.P.). Reflex sensitivity declines with increasing hypertension and with increasing age. (Extended from the data of Gribbin et al.[6])

directly. We have some evidence for this in the dog; particularly when larger doses of phenylephrine were used, the diameter of the carotid sinus *decreased* during a pressure increase.[11] Previously, Scher and Young[12] found no differences between the reflex effects of increases in blood pressure from an occluding cuff on the descending aorta and the effects of phenylephrine injections in the conscious dog.

A final criticism of the drug methods is that we cannot be certain that other receptors (such as cardiopulmonary receptors) are not involved in the responses. Despite these objections, the method has proved useful in elucidating changes in gain of the baroreflex arc both between subjects and within individual patients, to compare gain at rest with that on exercise[13–16] or during mental arithmetic,[17] anesthesia,[18] autonomic blockade[19,20] and hypoxia or hypercapnia.[21–23]

A broad measure of agreement now exists that the baroreflex in hypertensive human beings both is reset to a higher level and has diminished gain.[6–8,24] It seems likely that any exaggeration of the reflex caused by a direct action of phenylephrine on the sinus would be seen only when large doses are used and would be less obvious in older or hypertensive subjects in whom the carotid sinus wall is considerably sclerosed.[25,26]

Neck Cuff Methods

Previous methods have used arterial and venous cannulas, and it is therefore attractive to consider noninvasive methods. There has recently been renewed interest in the use of a neck cuff to decrease or increase the carotid transmural pressure. Eckberg and coworkers[27,28] in particular have made good use of this method to examine the carotid reflex control of heart rate. Their design of neck chamber is certainly the most comfortable and least cumbersome device so far in use; computer-controlled valves and pressures have enabled them to place stimuli at precise points in the cardiac cycle and to deliver single short (0.6 second) stimuli or trains of stimuli that can mimic the ramp changes obtained by pressor drugs.

With this device Eckberg[29] found that the adaptation of the reflex cardiac slowing in response to single step changes in pressure closely resembles that of single baroreceptor afferents in animals. He also found that maximal slowing occurred when the stimuli were delivered about 0.75 second before the next expected P wave. Moreover, he found that the response time of the system was short, averaging 0.24 second; this will, of course, allow one arterial pulse to influence the immediately following pulse interval.

One criticism leveled at the Oxford phenylephrine method of testing reflex sensitivity is that the gain appears to be closely related to the pretest heart rate; slower rates are associated with greater gain. Eckberg[30] showed that this relation probably occurred because the reflex gain was influencing the resting rate and not vice versa. In Figure 3 it can be seen that the slope (gain) of the response to neck suction does not depend on the starting pulse interval. Eckberg found that the normotensive human reflex response began to saturate, or reach a plateau, at transmural pressures greater than 160 mm Hg.

Blood pressure responses to neck cuff stimuli: Mancia et al.[31] have extended the neck cuff suction technique by examining in human beings the responses to neck pressure (that is, decreased carotid transmural pressure) in addition to neck suction. In addition to measuring the heart rate responses, they also measured the effect on arterial pressure; this cannot be examined by the phenylephrine technique. This advantage is to some extent balanced by two disadvantages: (1) The reflex effects caused by stimulation of the carotid receptors are simultaneously being buffered by aortic and other baroreceptors that will be sensing changes of opposing sign. (2) Pressure changes produced in the neck chamber are not fully transmitted through the neck to the carotid sinus itself; transmission of positive pressure averaged 86 percent, but neck suction only 64 percent.[32]

The Milan group[31] *first examined normotensive subjects* and found that the heart rate responses to changes in carotid transmural pressure were more transient than those found by Eckberg. They also found that changes in arterial pressure were greater for decreasing transmural pressure than for increasing pressure. This finding does not accord with data from animal experiments on the characteristics of carotid sinus receptors[33] or on reflex changes in conscious rabbits

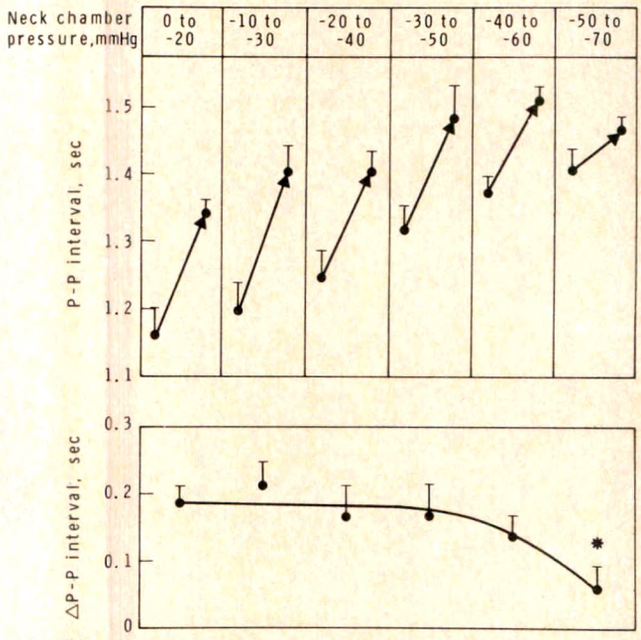

FIGURE 3. Averaged pulse interval responses to 20 mm decrements of neck chamber pressure superimposed on neck chamber pressures of 0, −10, −20, −30, −40 and −50 mm Hg. The average control pulse interval is shown on the left of each **upper panel,** and the average pulse interval occurring after neck suction is shown on the **right.** Pulse prolongation was comparable when 20 mm Hg neck suction was superimposed on ambient neck suction up to 40 mm negative, but was significantly less ($P < 0.001$) at −50 mm Hg (**lower panel**); at this level it appears likely that the receptors are maximally firing. (Reprinted by permission, from Eckberg.[30])

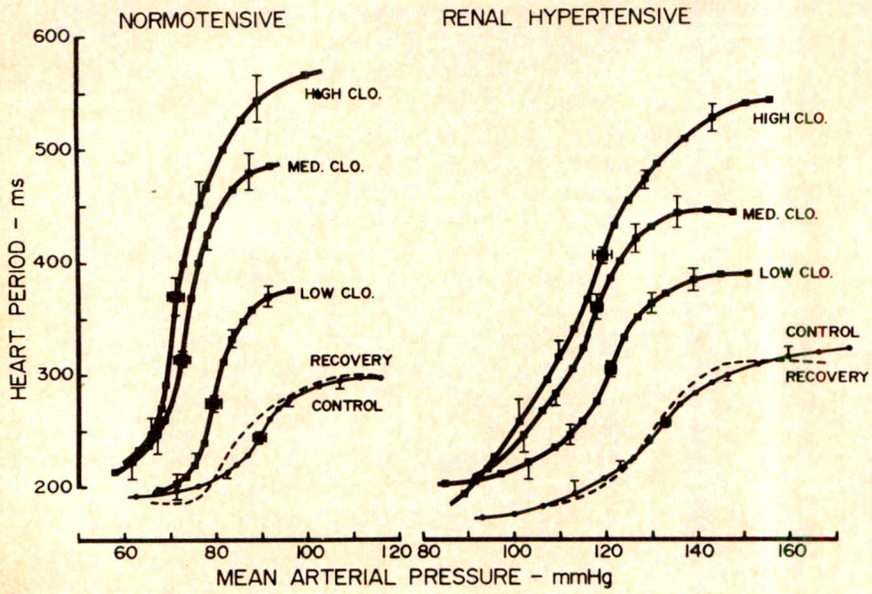

FIGURE 4. Baroreflex function curves obtained in conscious rabbits by manipulation of arterial pressure by balloon cuffs previously placed separately around the inferior vena cava and aorta. The curves are symmetric (for gain) around the set points for resting pressure and heart period (**closed squares**). The gain, set and range of the baroreflex were strikingly increased by small doses of clonidine (CLO.), injected into the lateral ventricle of the brain. (Reprinted by permission, from Korner et al.[34])

(Fig. 4).[34] It may represent interactions with other receptor areas or inadequate transmission of box pressures, as just discussed. These investigators also compared the neck box changes with the reflex effects of drugs (phenylephrine, nitroglycerin) and found a threefold increase in the reflex gain with drugs, which they attributed to the contribution of extracarotid baroreceptors. We[11] found a direct effect of phenylephrine on the carotid sinus smooth muscle, which might furnish an alternative or additional cause for the increase in sensitivity seen with drugs.

Use of the neck pressure technique in hypertensive subjects: Both Mancia et al.[35] and Eckberg[36] used the neck box method to examine the sensitivity of the baroreflex in hypertension. Eckberg studied 10 normotensive subjects (dividing line was a blood pressure level below 140/90 mm Hg) and compared heart rate responses in subjects with borderline pressures (sometimes above, sometimes below 140/90 mm Hg). Overall, the reflex of the subjects with borderline hypertension was reset to a slightly higher level than normal, but gain (sensitivity) was unchanged. However, those with the higher pressures also showed a significant decrease in gain, in keeping with the earlier studies using drugs.[6,8] Eckberg concluded that this finding provided support for the hypothesis that baroreflex dysfunction might cause hypertension.[1,37]

However, Mancia et al.,[35] who also examined the response of arterial pressure to carotid stimuli, found that the response to increases in transmural pressure was

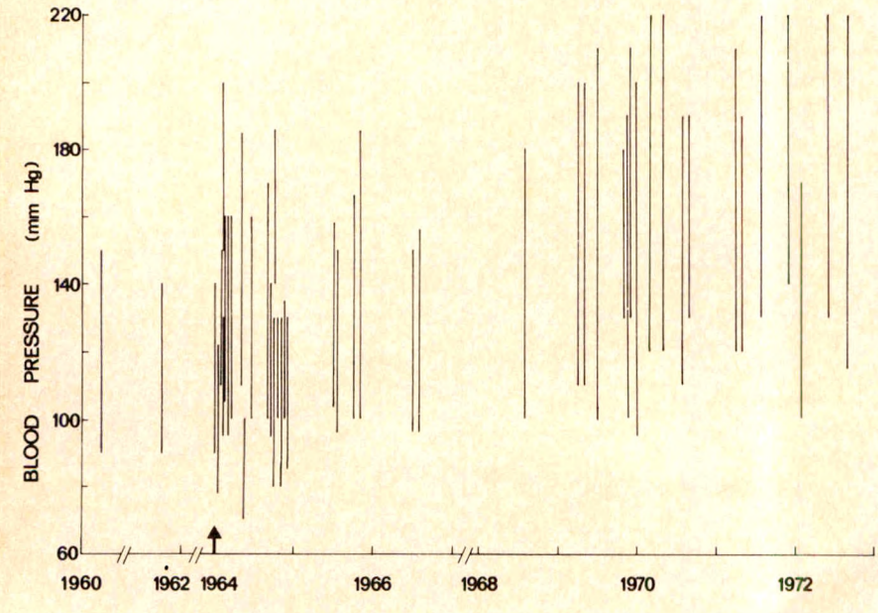

FIGURE 5. Blood pressure data of an asthmatic man who underwent carotid body (and incidentally sinus) denervation in 1964 at age 54 years (**arrow**). Blood pressure preoperatively was 120/80 mm Hg intraarterially; postoperative blood pressure was 200/120 mm Hg. Note the fluctuation in 1964, then the sustained hypertension.

different in hypertension. They had previously found that in normal subjects the reflex was most sensitive to decreases in carotid transmural pressure, whereas in patients with hypertension they found the reverse; that is, the reflex was more sensitive to increases in transmural pressure. They concluded that although in normal subjects the carotid reflex was more effective in protecting against hypotension, in hypertensive subjects it was more effective in combating hypertension. I find these results interesting but difficult to fit into what is known from animal studies. Certainly their results for heart rate responses are diametrically opposed to our own, using drugs, and to those of Eckberg,[36] using the neck chamber in subjects with borderline hypertension.

Relation Between Diminished Baroreflex Gain and Hypertension

Resetting: Since the classic experiments of McCubbin et al.,[38] it has been known that carotid baroreceptors are reset in hypertension. It was at first assumed that the receptors were functioning normally but at a higher "set" pressure. We[33] have reexamined the same question and find that as well as a resetting there is a diminution in sensitivity to change in pressure. I believe that this reduction in gain is important in the vicious circle of hypertension. Reduced gain is likely to lead to slower and less effective buffering of increases in pressure.

Could insensitive baroreflexes be causal in human hypertension?: It is impossible to be dogmatic on this point, but increasing evidence suggests this possibility. We have observed a subject with surgical denervation of the carotid sinuses who became severely hypertensive immediately postoperatively (Fig. 5). His pressures fluctuated greatly at first (rather like those of the Cowley and Guyton dogs), but gradually they came to resemble those of "essential" hypertension.

Hypertension increases with age, as does vascular degeneration in most western and urbanized societies. However, it is not an invariable progression in all societies, and it is tempting to speculate whether vascular sclerosis at the baroreceptor sites might initiate a slow loss of control of arterial pressure. Certainly we know from animal experiments[34] that hypertension itself can also cause loss of peripheral baroreceptor function and hence a slow vicious circle.

Sympathetic overactivity in hypertension: Recent evidence in human hypertension suggests increased sympathetic tone.[39] We[40] showed that subjects with poor baroreflexes respond to a standard exercise test with a greater increase in blood pressure and in the plasma noradrenaline level than do those with good reflexes (Fig. 6). This lends some support to the hypothesis that hypertension might be caused by poor buffering of the sympathetic nervous system by stiff arterial baroreceptors.

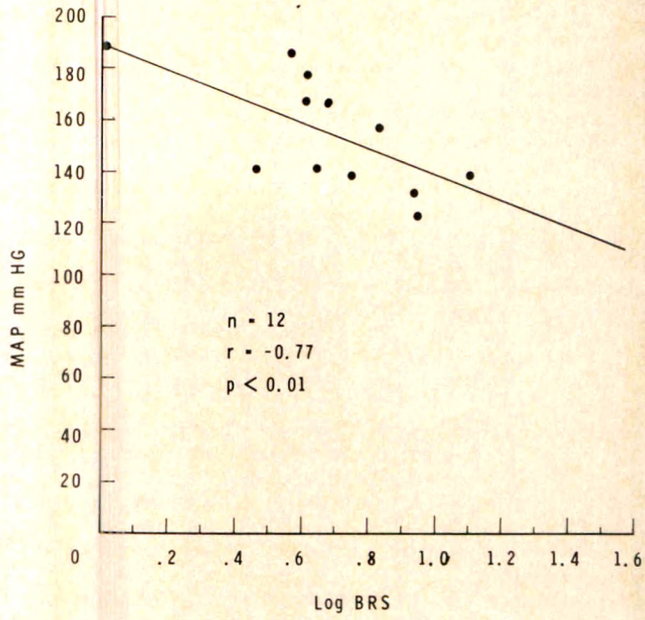

FIGURE 6. Relation between resting baroreflex sensitivity (BRS) and maximal arterial pressure (MAP) achieved during bicycling exercise in 12 subjects. The poorer the baroreflex, the greater the rise in blood pressure. (The same was true for plasma noradrenaline, not shown.) n = number of subjects; p = probability; r = correlation coefficient. (Reprinted by permission, from Floras et al.[40])

The effect of the mind: We[17] have recently studied the effect of confrontation or the defense reaction on blood pressure and the period of baroreflex control of the heart in man. We showed that during mental arithmetic the reflex is reset and its gain greatly decreased.

The future: It may be possible with noninvasive techniques, such as neck suction, to survey a population and determine if hypertension subsequently develops in those subjects who have poor baroreflex function.

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Control of Blood Pressure by Carotid Sinus Baroreceptors in Human Beings

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Most techniques available for studying arterial baroreflexes in man are unsuitable for analysis of the primary function of these reflexes, that is, arterial pressure control. Such control can be evaluated during increases and decreases in carotid baroreceptor activity obtained with a variable pressure neck chamber. This study reviews some technical aspects of the technique and describes the influence the carotid baroreceptors exert on arterial pressure in normotensive subjects and in those with essential hypertension. Major differences can be found in the two populations. In normotensive subjects the change in blood pressure is greater with a decrease than with an increase in baroreceptor activity. The former response becomes progressively less and the latter progressively greater with increasingly high blood pressure, so that in severe hypertension the reflex shows an asymmetry opposite to that in normotensive subjects, the change in blood pressure being greater with an increase than with a decrease in baroreceptor activity. These results imply that in human hypertension the carotid baroreflex mechanism controlling blood pressure undergoes a very marked resetting but shows no major reduction in sensitivity. In hypertensive subjects cardiac output and peripheral resistance were also measured. It was found that the depressor response to an increase in carotid baroreceptor activity depends on both a reduction in cardiac output and a systemic vasodilatation. However, peripheral vasoconstriction is the only factor accounting for the pressor response to reduced baroreceptor activity.

The primary function of arterial baroreceptors is to control arterial blood pressure. The modality and the extent of this control have been extensively investigated in experimental animals and are known in considerable detail.[1] However, little of this extensive knowledge has been controlled in human beings, the primary reason being the lack of proper methods of study. Several techniques are available for studying reflex control of circulation in human beings, but regrettably most are unsuitable for evaluation of the influence on blood pressure that is selectively exerted by the arterial baroreceptors. The technique that is most extensively used is based on alterations in activity of the arterial baroreceptors obtained by changing arterial blood pressure with the administration of vasopressor and vasodepressor drugs.[2,3] This allows study of the influence of arterial baroreceptors on heart rate and other cardiac functions,[4] but obviously it cannot offer any information on the reflex control of peripheral circulation and blood pressure. Another commonly used technique alters venous return to the heart with the Valsalva maneuver,[5] thus indirectly inducing changes in arterial blood pressure and baroreceptor activity. Although this technique allows some information to be obtained on reflex alterations in vascular resistance,[6] it relies mainly on reflex changes in heart rate; furthermore, the range of receptors involved in the Valsalva maneuver is much wider than that of the arterial baroreceptors, the low pressure receptors in the cardiopulmonary region being certainly and largely included.

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A third technique consists of the application of negative pressure to the lower half of the body to reduce central blood volume and, after a suitable increase of the stimulus, arterial blood pressure as well.[7] This allows measurement of reflex changes in several vascular beds as well as the heart and is certainly a valuable method for selectively studying reflexes originating from the cardiopulmonary area. However, with regard to the arterial baroreflexes, this technique is much less selective because, as with the Valsalva maneuver, the engagement of the arterial baroreceptors is preceded and accompanied by that of the low pressure receptors. Furthermore, the fact that alteration in baroreceptor activity is obtained through a mechanically induced reduction in arterial blood pressure prevents changes in this variable to be assessed precisely.

The Variable Pressure Neck Chamber

A fourth technique for investigating reflex control of the circulation in human beings is the variable pressure neck chamber. This consists of a tight rigid collar within which pneumatic pressure can be reduced in a graded fashion below atmospheric pressure, thereby producing an increase in transmural pressure across the carotid sinuses and an increase in carotid sinus baroreceptor activity. Several designs for this technique have been developed by various investigators.[8–12] In our own design[12] the collar encircles the neck from the shoulders to a plane approximately intersecting the lower part of the face and skull, so that alterations in transmural pressure are evenly produced around the entire circumference of the neck arteries. Furthermore, each end of the collar is provided with a double rubber valve system that allows pneumatic pressure inside to be changed not only in a negative but also in a positive direction; this makes it possible to produce a decrease as well as an increase in baroreceptor activity.

This technique offers several important advantages in the study of arterial baroreflexes. It addresses attention primarily to an arterial baroreceptor area, that is, the carotid sinus region, which is certainly of major importance. It allows estimation of peripheral vascular effects and heart effects and most importantly the final integration of these effects into blood pressure responses. It allows performance of the study over a range of baroreceptor activities, from those below to those above the level set by the existing blood pressure stimulus. However, there are some disadvantages. One is that alterations in blood pressure induced by the carotid sinus baroreceptors affect the activity of cardioaortic baroreceptor areas in a way that tends to oppose the primary carotid sinus effects. This factor has to be taken into account in interpretation of the reflex responses.

The studies that will be reviewed here refer to a series of investigations performed with our type of neck chamber. We will first touch on some technical points with regard to this method that had to be controlled in order to demonstrate its validity as a selective modulator of carotid baroreceptor activity and to quantify this modulation in a proper way. We will then describe blood pressure responses to increases and decreases in carotid baroreceptor activity in normotensive subjects and in patients with essential hypertension. Finally, we will mention the alterations in cardiac output and peripheral resistance induced by the carotid baroreflex in patients with hypertension.

Validation of the Neck Chamber Technique

Three aspects of the neck chamber technique could be subjected to an experimental control.[12] *The first* was that application of positive pressure to the neck may have reduced the pressure gradient from the arterial to the venous side of the head and that cerebral ischemia therefore participated in the production of the cardiovascular response. This possibility was excluded because application of positive neck pressures greater than those used in our studies (see later) did not produce any desaturation of the venous blood refluent from the brain, thereby suggesting that no reduction in cerebral blood flow occurred.[13]

The second aspect was that application of positive neck pressure may have reduced the pressure gradient from the arterial to the venous side of the carotid body circulation, thus producing ischemic activation of the chemoreceptors. This point was controlled by applying positive neck chamber pressures in a condition in which the chemoreceptors could not be easily stimulated by a reduction in carotid body blood flow, that is, when the arterial partial pressure of oxygen (PO_2) of the subject had been elevated above 500 mm Hg by breathing of pure oxygen.[14] The observed reflex increase in arterial pressure was no different from that observed in the control condition at normal arterial PO_2, suggesting no contribution of the chemoreceptors to the reflex effect. Similar evidence against involvement of a chemoreceptor reflex has also been obtained with application of negative neck chamber pressure.[11]

Third, we investigated the problem of tissue pressure transmission from the atmosphere of the neck chamber to that of the carotid sinus region. This aspect was of obvious importance because it dealt with the possibility of having a fair quantitation of the tissue pressure gradient acting on the reflexogenic area under study. Ten subjects (six with normal and four with elevated arterial blood pressure) were subjected to a series of different positive and negative pressures within the neck chamber while tissue pressure was recorded simultaneously from a small catheter inserted under local anesthesia through the skin of the neck to lie close to the carotid sinus wall. Three major results were found. First, there was a remarkably strict linear relation between changes in either positive or negative neck chamber pressure and changes in neck tissue pressure, the correlation coefficient being greater than 0.989 in each subject. Second, the pressure transmission from the neck chamber to the carotid sinus, although prompt and stable throughout the entire stimulus, was incomplete and lower for the negative than for the positive pressure; on average, 64 ± 3 percent of negative pressure was transmitted to the carotid sinus region whereas transmission of positive pressure amounted to 86 ± 2 percent. Third, the amount of

pressure transmission varied little from subject to subject and showed no relation at all to variables such as sex of the subject or shape and thickness of the neck. The aforementioned average figures could therefore be legitimately used as correction factors for the applied neck chamber pressures in all normotensive and hypertensive subjects under investigation, to obtain a more precise quantitation of the pressure stimuli that were imposed on the carotid sinuses.

Carotid Baroreceptor Influence on Blood Pressure in Normotensive Subjects

Carotid baroreceptor influence on blood pressure: This was first investigated in 11 normotensive subjects (mean age 36 ± 4 years) in whom blood pressure measurements were made with use of a femoral arterial catheter.[15] In each subject a series of four to six different negative pressures and a series of four to six different positive pressures were applied in a random order, their maximal value never exceeding ±50 mm Hg. Each pressure application was rapidly instituted and maintained constant for 2 minutes before being abolished at a similar rapid rate. The effects of neck pressure applications were evaluated by averaging values for mean arterial pressure that occurred both between the 5th and 15th second and between the 90th and 120th second after the beginning of the stimulus, a comparison being made with the average mean blood pressure value that was measured in the 30 seconds immediately preceding the stimulus. This allowed us to take into account both an early and a late response to alteration in carotid baroreceptor activity, thus providing a temporal analysis of the reflex effects. In each instance the magnitude of the applied neck pressure and the resulting early or late alterations in blood pressure were found to be in a significant linear relation, no flattening of the responses at the extreme neck chamber pressures ever being observed. Thus, the regression coefficients, that is, the slopes, of the relation could properly be taken as the measure of the magnitude of the reflex function. The results of this study in the 11 subjects are summarized in Figure 1.

The most important finding that emerged from these data was the existence of a difference between the effects of the decrease and the increase in carotid transmural pressure, the reflex alteration in blood pressure obtained with the decrease in carotid transmural pressure being significantly greater in each subject than that obtained with the increase. These results confirmed those obtained with a neck chamber by Thron et al.,[10] although in our study the more precise estimation of the negative pressure stimulus showed the asymmetry of the reflex to be less pronounced than that reported by Thron et al.[10]

Mechanisms of asymmetry in blood pressure response: Two hypotheses can be advanced. One is that in normotensive subjects, carotid baroreceptors discharge at basal blood pressure near their maximal level, thus allowing the decrease in baroreceptor activity induced by a decrease in carotid sinus transmural pressure to be greater than the increase in baroreceptor activity

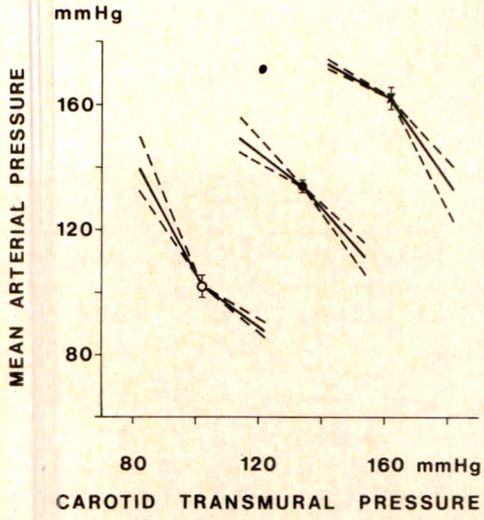

FIGURE 1. Carotid baroreceptor influence on blood pressure in 11 normotensive and 18 moderately hypertensive and 17 severely hypertensive subjects. The **open circle,** the **closed circle** and the **cross** represent the average (± standard error) mean arterial pressure during the control period in each group, respectively. The continuous lines represent the average of individual regression coefficients relating mean arterial pressure to increased and decreased carotid transmural pressure with respect to control values, the **dashed lines** indicating the standard errors of the regressions. The data are shown for the late or steady state effects of the neck chamber, the carotid transmural pressure being calculated as the difference between the mean arterial pressure and tissue pressure outside the carotid sinuses. The latter was calculated from the value of the neck chamber pressure variation after application of the correction factors for loss of pressure transmission through the neck tissues. (Redrawn by permission, from Mancia et al.[23])

induced by an increase in carotid transmural pressure.[10] This hypothesis is supported by studies in which the diameter of the neck arteries was measured at different blood pressure values. Because of their thin walls, the carotid sinuses were already almost maximally distended at physiologic blood pressure levels and showed diameter excursions with each pulse that were greater than those observed in the neighboring arteries. It is therefore conceivable that at normal blood pressures, near maximal baroreceptor activity may exist.[1]

A second hypothesis is that in normotensive subjects baroreceptors in the aortic arch discharge basally near their maximal level. In this case the depressor response induced by an increase in carotid baroreceptor activity would be more effectively buffered than the pressor response induced by a decrease in carotid baroreceptor activity, thus accounting for the asymmetry that we observed. However, three considerations make this hypothesis less likely than the preceding one. First, animal studies have never shown the aortic baroreceptors to be near maximally stimulated at normal blood pressure levels. On the contrary, available evidence suggests that myelinated fibers subserving these receptors are often barely at threshold at normal blood pressure levels,[16] a phenomenon that is even more evident for the nonmyelinated aortic baroreceptor fibers.[17,18] Second, in line with electrophysiologic evidence, animal studies also show that aortic baroreflexes

are engaged more by increases rather than by decreases in arterial pressure and that therefore they buffer the former blood pressure alteration to a much greater extent than the latter.[19,20] This point is also evident when blood pressure alterations are induced by the carotid baroreceptors.[21] In the dog, decreases in carotid sinus pressure induce a pressor response that becomes much greater after denervation of the cardioaortic baroreceptors. However, this procedure does not alter significantly the depressor response induced by increases in carotid sinus pressure. Third, evidence against an antihypotensive action of the aortic baroreceptors also was collected in normotensive subjects by Guz et al.[22] In their study anesthetic blockade of both cervical vagal nerves induced no increase in blood pressure, suggesting that no tonic inhibitory influence was exerted by the aortic baroreceptors on blood pressure and therefore that these receptors could not provide a counteracting action on a decrease in blood pressure.

In conclusion, it is likely that the asymmetry of the blood pressure responses to increases and decreases in carotid baroreceptor activity reveals an inherent property of the carotid baroreceptor function in human beings. This implies that this reflex mechanism can provide normotensive persons with a better antihypotensive than antihypertensive action.

Carotid Baroreceptor Influence on Blood Pressure in Essential Hypertension

Blood pressure control by the carotid sinus baroreceptors was investigated in 35 patients with untreated essential hypertension,[23] the study being performed exactly in the same manner as that for normotensive subjects. These patients were separated into two groups of 18 and 17 patients (mean age 43 ± 2 and 48 ± 2 years, respectively) according to whether the basal value of mean arterial pressure was below or above 145 mm Hg. These two groups were conventionally indicated as having "moderate" and "severe" hypertension. The results are shown in Figure 1 as regression coefficients of alterations in mean arterial pressure on carotid

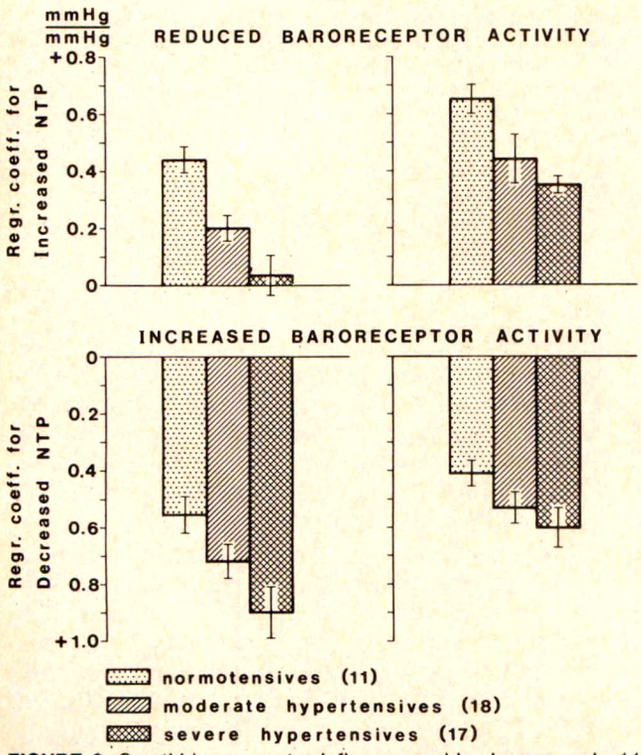

FIGURE 2. Carotid baroreceptor influence on blood pressure in 11 normotensive and 18 moderately hypertensive and 17 severely hypertensive subjects. The data are shown as the average (±standard error) of individual regression coefficients (Regr. coeff.) relating changes in mean arterial pressure (mm Hg) to changes in tissue pressure outside the carotid sinuses (NTP, mm Hg). Data for increased NTP, that is, reduced baroreceptor activity, are shown **at top;** data for decreased NTP, that is, increased baroreceptor activity, **at bottom;** both early (**left panels**) and late or steady state (**right panels**) responses are represented. Notice that regression coefficients were always positive as increased NTP induced increases in blood pressure and vice versa. (Redrawn by permission, from Mancia et al.[23])

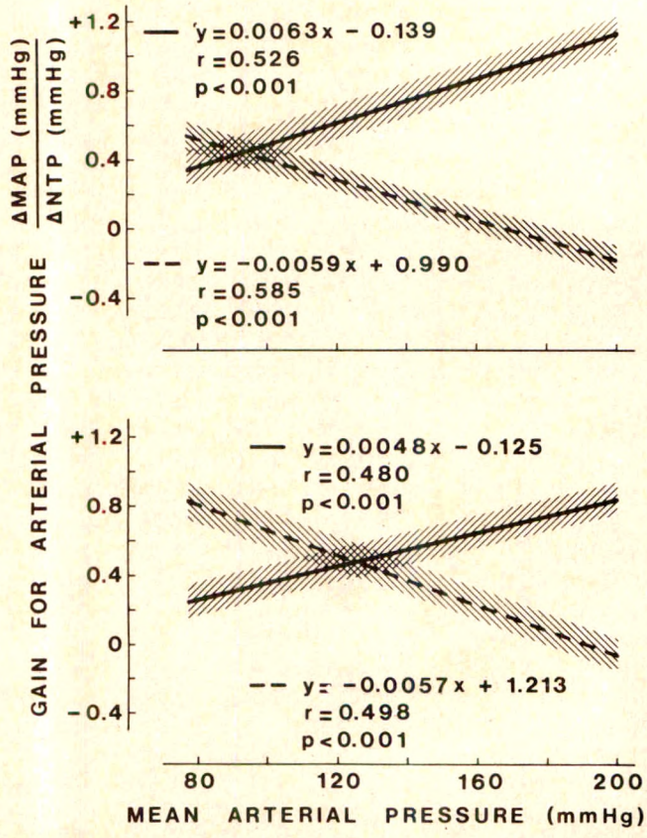

FIGURE 3. Relation between gains of the carotid baroreflex and basal mean arterial pressure in 11 normotensive and 35 hypertensive subjects. The gain of the reflex is expressed as changes in mean arterial pressure (MAP) induced by changes in tissue pressure outside the carotid sinuses (NTP); the early response is shown in the **upper panel** and the late response in the **lower panel.** (For details see text.) Gains for increased baroreceptor activity are indicated by the continuous lines, gains for reduced baroreceptor activity are indicated by the **dashed lines,** and the **hatched areas** represent the standard errors of the regressions. There were always significant linear regressions between the gain of the baroreflex and the value of basal mean arterial pressure. The equations of the regression are shown. p = probability; r = correlation coefficient.

transmural pressure, during the late part of the neck chamber stimulus. A comparison among the normotensive, moderately hypertensive and severely hypertensive groups is also shown in Figure 2, in which the regression coefficients indicate the alterations in mean arterial pressure induced by the alterations in tissue pressure outside the carotid sinuses, both the early and the steady state responses to the neck chamber being represented. Clearly, major differences existed among the reflex functions in the normotensive subjects and in the two groups of hypertensive patients. The pressor response to reduction in carotid transmural pressure was maximal in the normotensive group and decreased progressively in the groups with moderate and severe hypertension. However, the depressor response to increases in carotid transmural pressure showed an almost exactly opposite pattern; that is, it was minimal in normotensive subjects and increased progressively to achieve its maximal value in the group with severe hypertension.

These changes also appeared when the reflex functions were plotted in continuum on basal values of mean arterial pressure, if the normotensive subjects and the hypertensive patients were considered as a single population. This point is shown in Figure 3 in which the basal values of mean arterial pressure are indicated on the abscissa while the magnitude (or gain) of the reflex function is indicated on the ordinate as the reflex change in mean arterial pressure induced by the change in tissue pressure outside the carotid sinuses. The continuous lines refer to the condition of increased carotid baroreceptor activity and the dashed lines to the condition of decreased carotid baroreceptor activity. Both the early (upper panel) and the late (lower panel) responses to application of the neck chamber are shown. In all cases the reflex effects were in a significant linear relation to the basal values of mean arterial pressure. The relation was positive for the effects of increased baroreceptor activity and negative for the effects of reduced baroreceptor activity; that is, the former response increased progressively and the latter decreased progressively as the basal mean arterial pressure of the whole group of subjects changed from the lowest normotensive to the highest hypertensive value. As a result, the asymmetry of the reflex response that was present in normotensive subjects (that is, a greater response to a decrease than to an increase in carotid baroreceptor activity) was first abolished and then reversed in hypertensive subjects who showed a progressively greater asymmetry in an opposite direction (that is, a greater response to an increase than to a decrease in carotid baroreceptor activity). In severely hypertensive subjects this reverse asymmetry became so marked that sometimes only large responses to an increase with no responses to a decrease in baroreceptor activity were observed. An example of this finding in a subject with very severe hypertension is shown in the original tracing of Figure 4.

Mechanisms of blood pressure responses: Several questions raised by these data cannot undergo experimental control in human subjects. However, a plausible hypothesis can be advanced to explain two main findings. The first finding is the reversed asymmetry that the carotid baroreflex showed in normotensive and hypertensive subjects. Figure 1 suggests that this reversed asymmetry occurred because blood pressure became paradoxically a progressively less effective stimulus for the carotid baroreceptors as we proceeded from normotensive subjects to those with moderate and severe hypertension. In other words, in normotensive

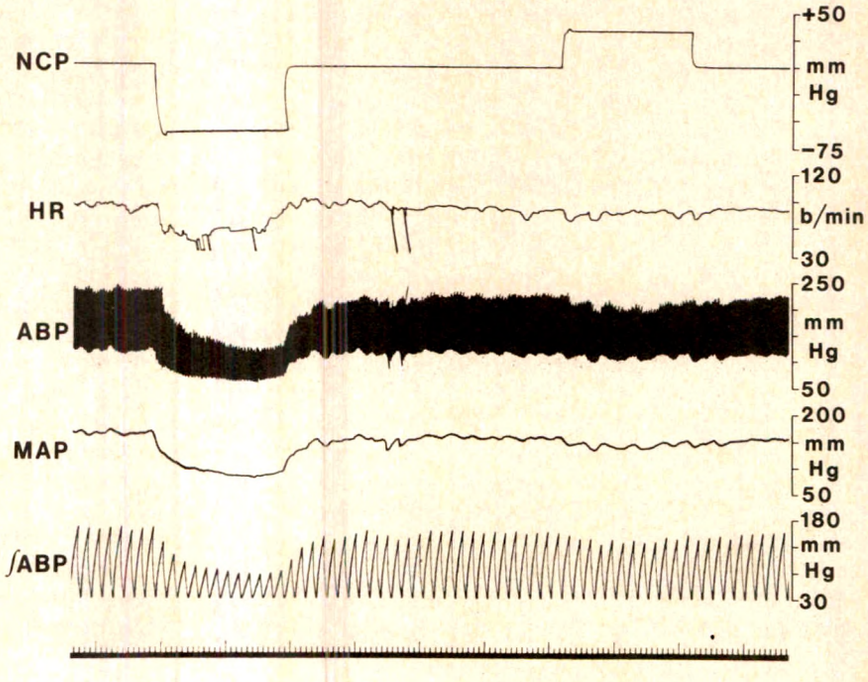

FIGURE 4. Original tracing of the hemodynamic changes induced by a decrease and an increase in neck chamber pressure in a severely hypertensive subject. ABP = pulsatile arterial blood pressure; HR= heart rate; MAP = mean arterial pressure; NCP = neck chamber pressure; ∫ ABP = blood pressure integrated over consecutive 10 second periods. Time lines at bottom are 1 and 5 seconds.

subjects basal blood pressures were capable of inducing a near maximal baroreceptor activation, thereby allowing large decreases but only small further increases in the receptor activity to occur with the use of the neck chamber. In hypertensive subjects the stimulus provided by basal blood pressure became progressively less effective and finally it was just above the baroreceptor threshold. Under these circumstances smaller decreases but larger increases in the receptor activity were obtainable with a neck chamber. Explanations for this finding can be found in several animal studies on experimental hypertension. These studies showed that in hypertension the stiffness of arterial walls and perhaps the alteration in the baroreceptor properties increase the pressure threshold and the pressure operating range of the baroreceptors,[24] a phenomenon that becomes more evident as hypertension progresses in intensity and duration and is known as baroreceptor "resetting" in hypertension.[25–28] The long duration of human hypertension (certainly longer in our subjects than in most experimental hypertension models) makes it conceivable that the resetting was so marked that even very high levels of basal blood pressure were capable of providing only a slight baroreceptor stimulus.

A second important finding is the baroreceptor sensitivity in human hypertension. Conclusive evidence has been produced that in hypertensive subjects arterial baroreceptor control of heart rate is less than that observed in normotensive subjects.[2,23,29] However, on examining our data on carotid baroreceptors, a reduction in sensitivity of blood pressure control does not appear to be as clear. The sensitivity of a baroreflex function must be taken from the slope of the steepest part of its sigmoidal stimulus-response curve.[30] This steepest part is probably that obtained in normotensive subjects by reducing carotid baroreceptor activity and in severely hypertensive subjects by increasing carotid baroreceptor activity. These two slopes appear similar (Fig. 1), suggesting that the sensitivity was similar in the two conditions.

Baroreceptor control of blood pressure versus heart rate: This unchanged sensitivity of the carotid baroreceptor influence on blood pressure in hypertensive subjects may in part be due to an impairment of the aortic baroreceptors, with a reduced buffering action of this reflexogenic area on the carotid baroreceptor response. However, attention should be directed to another possibility—that in human hypertension baroreceptor control of blood pressure may be much better preserved than baroreceptor control of heart rate. We can only speculate on the mechanisms of this preservation. Afferent baroreceptor firing is reduced in hypertension, at least with regard to its myelinated component.[27] However, the ultimate function of the baroreflex depends also on other components of the reflex arch, such as the centers, the efferent paths and the vascular effectors, all of which may be altered in hypertension in a manner to compensate for the primary reduction in baroreceptor signal. For example, Folkow et al.[31] showed that in early hypertension the arterioles present an increased wall to lumen ratio that makes the changes in vascular resistance in response to a given alteration in sympathetic outflow greater than those observed in normal vessels. It is possible that this peripheral factor amplifies the vascular responses, compensating for the reduced ability of the baroreceptors to modulate the sympathetic activity and maintaining the blood pressure response relatively unimpaired.

In conclusion, we suggest that in human hypertension baroreceptor control of blood pressure shows an extremely marked resetting phenomenon that brings the stimulating action of the existing pressure values from near baroreceptor saturation (as is the case in normotensive subjects) to near the baroreceptor threshold. We also suggest that the drastic reduction in baroreceptor sensitivity that has been described for regulation of heart rate in hypertension may be peculiar to this variable and that such a phenomenon may not occur to a large degree in baroreceptor control of blood pressure.

Carotid Baroreceptor Influence on Cardiac Output and Total Peripheral Resistance in Essential Hypertension

In 27 patients with untreated essential hypertension (mean age 45 ± 1 years) we investigated whether the blood pressure alterations induced by increases and decreases in carotid baroreceptor activity were due to alterations in cardiac output, vasomotor changes in systemic resistance vessels, or both. Cardiac output was measured with the thermodilution method.[32] A catheter with a terminal thermistor was introduced percutaneously into a femoral vein and its tip was positioned just beyond the origin of the right or left pulmonary artery. In less than 4 seconds, 10 ml of saline solution at 0° C was injected into the right atrium through the catheter so that the changes in temperature of the blood could be sensed by the thermistor after mixing in the right ventricle. The signal provided by the thermistor was elaborated by a digital computer to give actual values for cardiac output. The cardiac output measurements were made during the 30 seconds before the application of a positive and a negative neck pressure and during the last 30 seconds of each of these two stimuli. Total peripheral resistance was calculated by dividing mean arterial pressure during the time of injection by cardiac output values. Average stroke volume was calculated by dividing cardiac output by heart rate.

The results of these studies are shown in Figures 5 and 6. When a negative neck chamber pressure was applied (Fig. 5), that is, when carotid baroreceptors were activated above the existing level, the resulting reflex hypotension was accompanied by a significant reduction in both cardiac output and total peripheral resistance. The reduction in cardiac output was accompanied by a reduction in heart rate and stroke volume, although the latter change did not achieve statistical significance.

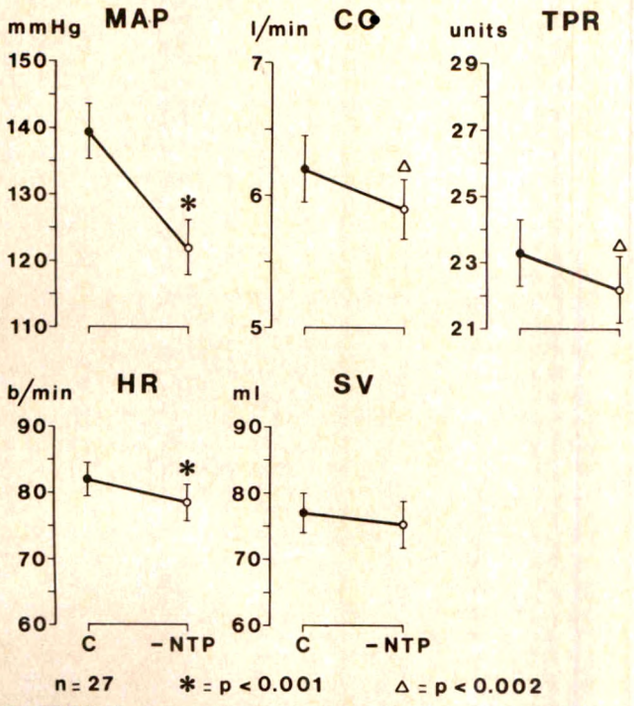

FIGURE 5. Hemodynamic responses to activation of the carotid baroreceptors by application of negative pressure (−35 ± 1 mm Hg) within the neck chamber. Data are shown as means ± standard errors in 27 subjects with essential hypertension. The **filled circles** indicate control values (C), the **open circles** values during the last 30 seconds of the baroreceptor stimulus (−NTP). The magnitude of the applied negative pressure is indicated as the value of this pressure outside the carotid sinuses (neck tissue pressure) which was obtained by correcting negative neck chamber pressures for loss of pressure transmission through the neck tissue. (See text.) MAP = mean arterial pressure; CO = cardiac output; TPR = total peripheral resistance; HR = heart rate; SV = stroke volume.

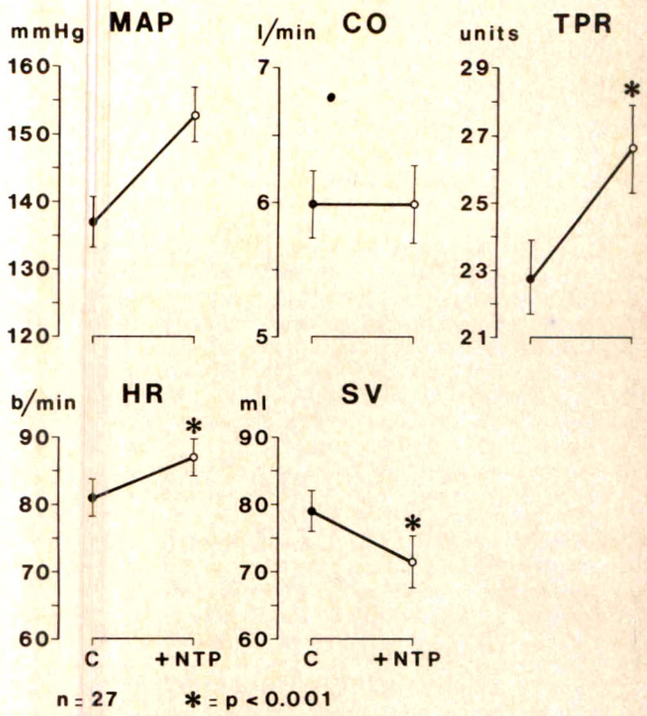

FIGURE 6. Hemodynamic responses to reduction in the activity of the carotid baroreceptors by application of positive pressure (+33 ± 1 mm Hg) within the neck chamber. Data are shown as means ± standard errors in the same 27 subjects of Figure 5. The **filled circles** indicate control values, the **open circles** values during the last 30 seconds of the reduction in the baroreceptor stimulus (+NTP). The magnitude of the positive pressure applied is indicated as the value of this pressure outside the carotid sinuses (neck tissue pressure) which was obtained by correcting positive neck chamber pressures for loss of pressure transmission through the neck tissues. All other symbols are the same as those in Figure 5.

When positive neck chamber pressure was applied (Fig. 6), that is, when the carotid baroreceptor stimulus was reduced below the existing level, the resulting reflex hypertension was accompanied by no change in cardiac output and by a significant and marked increase in total peripheral resistance. Cardiac output did not change because, although heart rate showed a significant increase, this effect was counteracted by a significant decrease in stroke volume.

Normotensive versus hypertensive subjects: The foregoing data must be compared with data on the effects of alterations in carotid baroreceptor activity on cardiac output and total peripheral resistance in normotensive subjects. In several studies on these subjects carotid baroreceptors were activated by the neck chamber[8,9,33,34]; the results were somewhat different from study to study but on the whole they showed that the carotid baroreceptor stimulation caused a reduction in both cardiac output and total peripheral resistance, the reduction in total peripheral resistance being perhaps more evident in younger persons.[35] Therefore, there is a substantial similarity between these hemodynamic responses to carotid baroreceptor activation in normotensive and hypertensive subjects insofar as both groups owe their hypotensive effect to both cardiac depression (see the bradycardiac effect) and systemic vasodilatation.

A difference, however, seems to materialize on considering the responses to a decrease in carotid baroreceptor activity by application of positive neck pressure. In this case the only available report[33] on normotensive subjects attributes the reflex pressor effect mainly to an increase in cardiac output with only some contribution to an increased peripheral resistance. However, in our hypertensive subjects the pressor effect was entirely attributable to peripheral vasoconstriction whereas cardiac output did not change despite the occurrence of tachycardia. The reduced contribution of cardiac output to the reflex pressor response may reflect a certain degree of reduction in cardiac function in hypertensive subjects, who may be less capable of increasing cardiac output in the presence of an increased afterload. A similar difference can be observed for the hemodynamic effects of isometric exercise in normotensive subjects and in subjects with heart disease or hypertension.[36–38]

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Integration of Reflex Responses in the Control of Blood Pressure and Vascular Resistance

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This overview presents four important concepts related to integration of cardiovascular reflexes. (1) Activation of sympathetic efferent activity to various organs is nonuniform. Simultaneous activation of both sympathetic and parasympathetic efferent pathways may occur. These effects are evident in the responses to diving and stimulation of chemoreceptors. Both diving and stimulation of chemoreceptors decrease heart rate and myocardial oxygen demand and cause intense peripheral vasoconstriction, which limits oxygen delivery to the periphery. Stimulation of chemoreceptors also causes active coronary vasodilatation favoring an optimal distribution of blood flow to the heart.

2. When two groups of sensory afferents that cause opposing responses are activated simultaneously, the effect of one sensory afferent system will override the other. During hypotension caused by occlusion of the circumflex coronary artery, the reflexes originating in cardiac vagal afferents are inhibitory and reverse the effect of unloading of arterial baroreceptors. The net effect is not simply blockade of sympathetic vasoconstrictor effects, but withdrawal of sympathetic tone. Thus, the cardiac "reflex" overrides the effects of arterial hypotension.

3. The reflex response to activation of one group of sensory afferents may be dependent on the input from other groups of afferents to the medullary neurons. At low carotid sinus pressure, the "gains" of the chemoreceptor and somatic reflexes are augmented. The cardiopulmonary vagal afferents modulate the arterial baroreceptor reflex as well as the chemoreceptor and somatic reflexes. The cardiopulmonary vagal afferents, when activated, suppress the sympathetic excitatory response to arterial hypotension, to chemoreceptor stimulation and to somatic afferent stimulation. Another important interaction is that of the thermal receptors which, when activated by heat, suppress the vasoconstrictor response to arterial hypotension in cutaneous more than in muscular beds.

4. Stimulation of sensory afferent receptors may be modified by drugs or humoral factors acting on the receptor itself or on the chemical and mechanical characteristics of the tissues surrounding the receptor. Acetylstrophanthidin injected into the circumflex coronary artery potentiates the sympathetic inhibitory response to activation of cardiac sensory afferents (vagal afferents) by volume loading and by occlusion of the circumflex. The sensitization may explain in part the action digitalis has on the peripheral circulation in heart failure.

The clinical implications of these four important physiologic concepts are discussed.

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An understanding of reflex regulation of vascular resistance and blood pressure requires the ability to integrate responses observed in several organs and vascular beds during activation of more than one type of sensory afferent. There are two reasons for this: (1) Reflex responses in various vascular beds are different and this difference determines the

optimal distribution of blood flow. (2) In the intact animal or human being, particularly in abnormal states, several groups of sensory afferents are activated simultaneously and the net reflex response cannot be deduced from knowledge of responses to activation of each group of afferents separately. For example, in hemorrhagic shock, arterial and cardiopulmonary baroreceptor reflexes as well as chemoreceptor reflexes are activated simultaneously when patients are hypotensive, hypoxic and acidotic. The net response does not equal the algebraic sum of responses observed when each reflex is activated alone. This nonlinear summation implies an "interaction of reflexes" that is important in circulatory control.

The experiments selected for presentation emphasize four concepts in the study of integrated control of the circulation: (1) selectivity and nonuniformity; (2) simultaneous activation of opposing reflexes; (3) interaction of reflexes; and (4) "sensitization" of afferent receptors.

Selectivity and Nonuniformity of Sympathetic Activity

Sympathetic neural activity to various vascular beds and even to segments of the same vascular bed is modulated in a nonuniform manner. The different components of the circulation are controlled selectively.[1,2] Furthermore, activation of the sympathetic outflow is not always accompanied by inhibition of the parasympathetic outflow and vice versa. There are reflex responses that include activation of the sympathetic and parasympathetic efferents simultaneously.

The following are several examples of selectivity and nonuniformity of neural control:

Differential responses of various vascular beds: Stimulation of chemoreceptors causes neurogenic vasoconstriction in skeletal muscle and in splanchnic and renal vessels, and vasodilatation in the coronary circulation, but there is no neurogenic influence on cerebral vessels.[3–6] The coronary vasodilatation is caused by activation of vagal parasympathetic efferents[5] and the constriction in other vessels is caused by activation of sympathetic adrenergic efferents. Thus, the neurogenic adjustment to stimulation of chemoreceptors favors the distribution of blood flow toward organs critically dependent on oxygen for their integrity and away from those relatively less dependent on oxygen.

Simultaneous activation of sympathetic and parasympathetic efferents: Diving and stimulation of chemoreceptors activate sympathetic efferents to the peripheral circulation causing intense vasoconstriction and parasympathetic efferents to the heart.[7] Marked bradycardia is seen during diving and during stimulation of chemoreceptors if the hyperventilatory response is prevented by artificial ventilation of the experimental animal. Peripheral vasoconstriction favors "oxygen delivery" to the coronary circulation and, when this is coupled with a reduction in myocardial oxygen demand as a result of bradycardia, the protective effect of the reflex is optimal. Recently, deBurgh Daly et al.[8] demonstrated that sustained bradycardia in the diving seal is caused by activation of the chemoreceptor reflex and Blix et al.[9] showed that the diving bradycardia is sustained in the duck by activation of cardiac vagal afferents as a result of intense peripheral vascular constriction and a shift of blood volume toward the cardiopulmonary region.

Differential responses to activation of two "inhibitory" reflexes in human beings: The stretch of arterial baroreceptors during hypertension and of atrial and ventricular receptors during hypervolemia increases their activity. Afferent impulses originating in these regions inhibit sympathetic vasomotor neurons and activate vagal nuclei. Conversely, a decrease in arterial blood pressure and hypovolemia or hemorrhage unload these receptors and cause a reflex increase in sympathetic and a decrease in vagal efferent activity. Although the afferent nerves from these two receptor regions project to the nucleus tractus solitarius, the physiologic responses to their activation or unloading are not identical, suggesting that they do not converge on the same neurons in the medulla.

We are able to evaluate the role of cardiopulmonary afferents and that of carotid baroreceptor afferents separately in human beings by applying "lower body negative pressure" using a suction box placed around the lower limbs to the level of the iliac crest. Suction with a commercial vacuum cleaner allows negative pressures of −5, −10, −20 and −40 mm Hg in the box. Progressive pooling of blood in the lower limbs during graded suction reduces central venous pressure and cardiac size. During minimal levels of lower body negative pressure (−5 and −10 mm Hg) central venous pressure decreases by 3 to 5 mm Hg but without a change in arterial pressure or heart rate; thus the signal sensed by the arterial baroreceptors is unchanged. Nevertheless, significant reflex vasoconstriction of forearm blood vessels and a reduction in forearm blood flow occur. The increase in forearm vascular resistance without a change in arterial pressure and without tachycardia (on occasions a decrease in heart rate of 2 to 3 beats/min is seen) suggests that the reflex is not caused by inhibition or unloading of arterial baroreceptors, but rather by unloading of cardiopulmonary baroreceptors[10] (Fig. 1).

When lower body negative pressure is applied at −40 mm Hg, arterial pressure decreases and pulse pressure narrows. Excessive pooling invokes the arterial baroreceptor reflex in addition to the cardiopulmonary reflex and the resulting response includes tachycardia, a slightly greater increase in forearm resistance (Fig. 1) and significant splanchnic vasoconstriction.[11,13] The results suggest that in human beings arterial baroreceptors regulate significantly heart rate and splanchnic resistance vessels but not forearm vessels, whereas the cardiopulmonary receptors regulate predominantly resistance of forearm vessels.

In order to evaluate more directly the role of carotid baroreceptors in man, a suction device is applied around the neck and the negative pressure increases carotid transmural distending pressure. Reflex bradycardia and hypotension occur but there is no significant

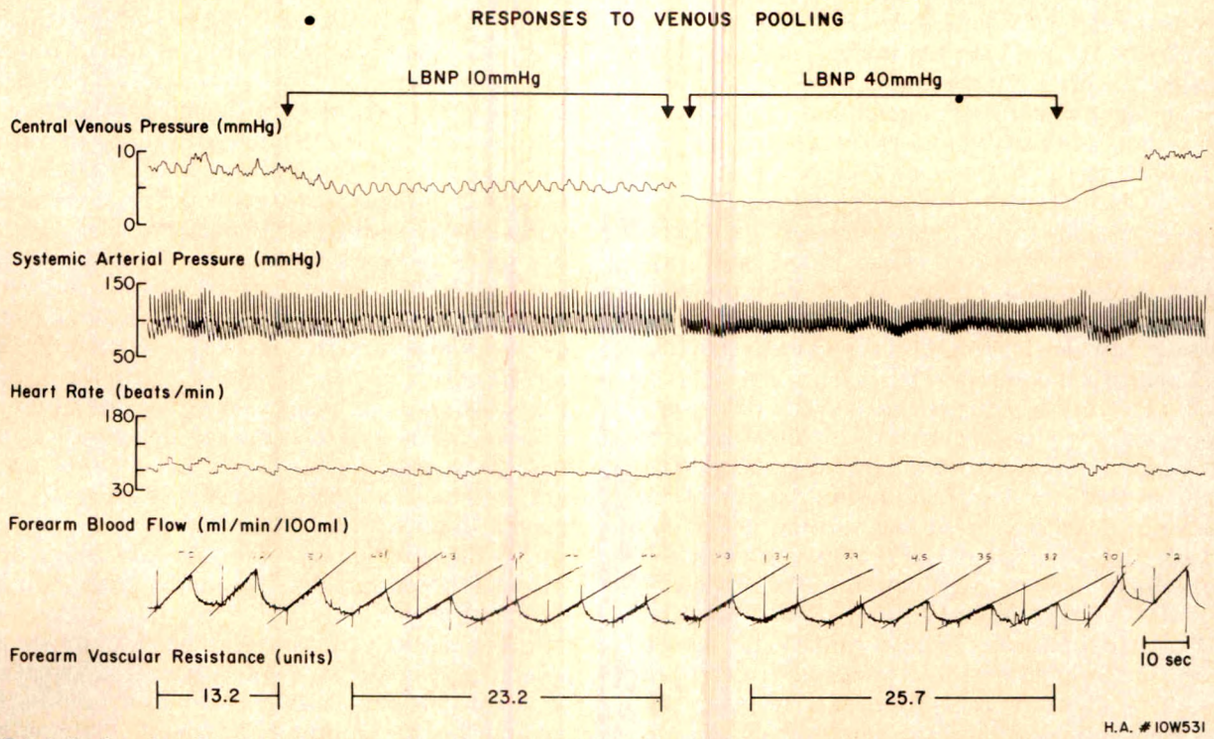

FIGURE 1. Activation of cardiopulmonary baroreceptor reflex in man. Minimal lower body suction with a lower body negative pressure (LBNP) of −10 mm Hg causes constriction of vessels of the forearm without any change in arterial pressure, pulse pressure or first derivative of pressure (dP/dt); there is no tachycardia. This reflex (**left half of figure**), which is thought to be mediated through low pressure cardiopulmonary receptors, as indicated by the decrease in central venous pressure, differs from the reflex induced during excessive pooling at LBNP of −40 mm Hg, which causes systemic hypotension and tachycardia but no vasoconstriction (**right half of figure**).

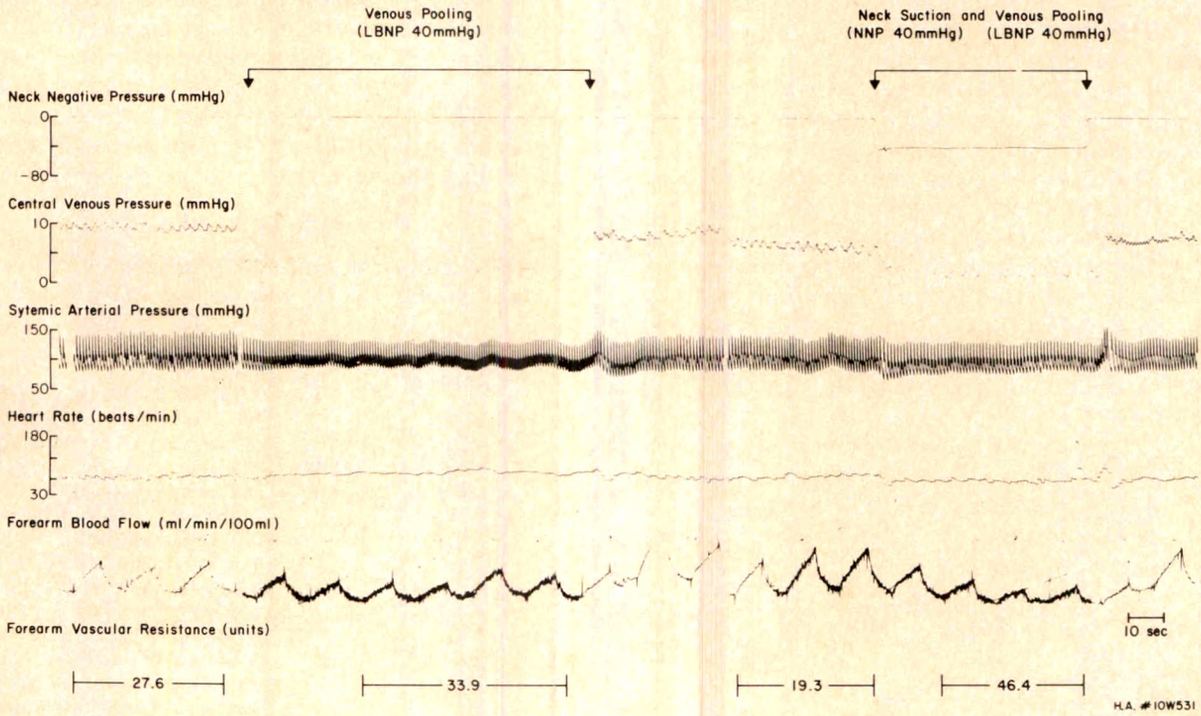

FIGURE 2. Comparison of the role of cardiopulmonary baroreceptors and carotid baroreceptors in the regulation of circulation in man. High levels of lower body negative pressure (LBNP) caused the decrease in central venous pressure, hypotension, reflex tachycardia and forearm vasoconstriction. When lower body negative pressure at high levels (LBNP 40 mm Hg) was applied simultaneously with carotid neck suction (NNP 40 mm Hg) (the latter to inhibit the input from the carotid baroreceptor reflex), the interaction resulted in a disappearance of the reflex bradycardia, but the reflex vasoconstrictor response was sustained.

decrease in forearm vascular resistance, thus confirming the belief that carotid baroreceptors do not modulate sympathetic efferents to resistance vessels of the forearm in human beings.[2,14] It is possible, however, that forearm vessels do not dilate during neck suction because sympathetic tone is very low to begin with in these subjects. When sympathetic tone is increased by excessive lower body negative pressure, forearm and splanchnic resistance vessels constrict and heart rate increases. Under these circumstances, simultaneous neck suction suppresses the reflex tachycardia and splanchnic vasoconstriction but the vasoconstriction in the forearm is unaltered[11,15] (Fig. 2).

These results demonstrate that the two inhibitory reflexes, namely, the carotid and cardiopulmonary reflexes in man, have selective influences on sympathetic efferents to various parts of the circulation. The carotid sinus reflex regulates heart rate and splanchnic resistance and has minimal effect on vessels of the forearm, whereas the cardiopulmonary reflex modulates sympathetic efferents to resistance vessels of the forearm. This situation is different from that in the dog where the same change in muscle resistance is associated with a greater change in renal resistance and heart rate in response to stimulation of cardiac vagal afferents as compared with stimulation of arterial baroreceptor afferents.[12]

Simultaneous Activation of Opposing Reflexes

In pathologic states, several groups of sensory afferents are activated simultaneously and their effects are synergistic. There are instances in which two groups of sensory afferents that cause opposing responses are activated simultaneously. An important question is whether the net effect will be "zero" or whether the effect of one sensory afferent will override the other. Following are three examples of conditions in which opposing reflexes are triggered simultaneously. Cardiac sensory afferents, which reflexly inhibit sympathetic drive, are stimulated (1) by inflation of a balloon in the ascending aorta causing acute left ventricular distension,[16] (2) by occlusion of the circumflex coronary artery causing ischemia of the posterior wall of the ventricle,[17] or (3) by coronary arteriography.[18] Simultaneously, arterial hypotension reduces the activity of arterial baroreceptors and increases sympathetic drive. The results in these three instances indicate that the net response is inhibition of sympathetic outflow with vasodilatation of the perfused skeletal muscle, decrease in renal nerve activity or bradycardia. Thus, the "cardiac reflex" overrides the effects of arterial hypotension.

Figure 3 illustrates the change in renal activity during hypotension induced by transient occlusion of the left anterior descending and circumflex coronary artery sequentially. Occlusion of the left anterior descending coronary artery caused hypotension and an increase in renal nerve activity. In contrast, occlusion of the circumflex coronary artery caused greater hypotension, bradycardia and a *reduction* in renal nerve activity in more than half of the animals studied despite the hypotension and intact sinoaortic nerves.[19] In these animals, the cardiac reflex triggered by circumflex arterial occlusion overrides the effect of inhibition of arterial baroreceptor activity during arterial hypotension. After sinoaortic denervation, the influence of arterial hypotension is minimized and the inhibitory effect of the "cardiac reflex" becomes much more pronounced.[19] Although evident with occlusions of both the circumflex and left anterior descending artery, it is more pronounced with circumflex occlusion. The greater inhibitory reflex response during occlusion of the circumflex than during occlusion of the left anterior descending artery reflects a greater density of cardiac sensory receptors with vagal afferents in the posterior wall of the left ventricle. The reflex is mediated through vagal afferents because after bilateral vagotomy there is lesser hypotension and a slight increase in the sympathetic nerve activity during occlusion of both left anterior descending and circumflex arteries.[19]

Interaction of Reflexes

The output from neurons in the medullary centers along the sympathetic and parasympathetic efferent

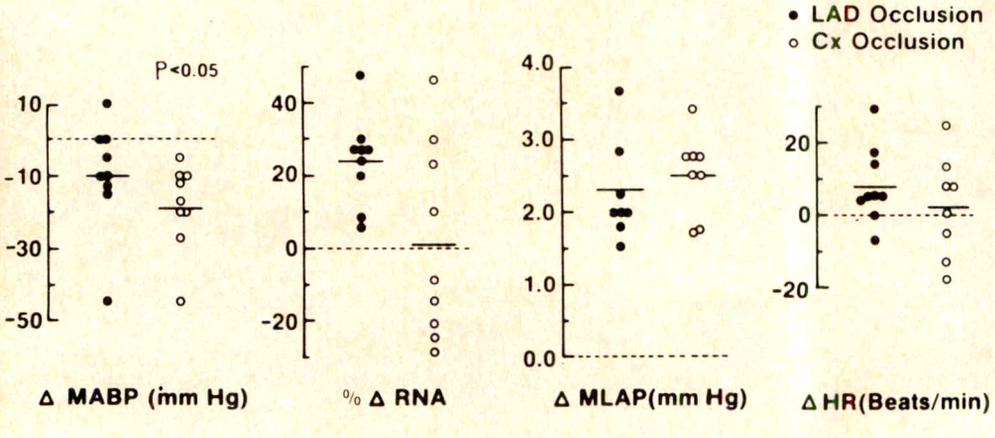

FIGURE 3. Occlusion of the left circumflex (Cx) and left anterior descending (LAD) coronary arteries causes similar increases in mean left atrial pressure (MLAP) but the decrease in mean arterial pressure (MABP) is greater with left circumflex occlusion. Despite the greater decrease in pressure there are several experiments where renal nerve activity (RNA) and heart rate (HR) decrease during left circumflex occlusion. After sinoaortic denervation, occlusions of the left circumflex and left anterior descending coronary arteries both reduce renal nerve activity and mean left atrial pressure but the reductions are much greater with occlusion of the former. P = probability.

pathways is constantly modulated by afferent input from various sensory receptors in the cardiovascular system and other parts of the body. Sensory afferent impulses originate in baroreceptors such as the arterial or cardiopulmonary baroreceptors or in receptors concerned with *oxygen conservation and delivery* such as the chemoreceptors, the trigeminal sensory afferents that mediate the "diving reflex," and the somatic receptors activated during exercise. Other receptors in the skin and in the hypothalamic region are sensitive to temperature. The medullary neurons are also under the control of spinal afferents from various viscera and afferents from various regions of the brain such as the hypothalamus, cerebellum, fastigial nuclei and cortex. These reflexes essentially subserve three functions: (1) maintenance of arterial pressure; (2) delivery of oxygen and nutrients to vital organs or to organs with increasing oxygen demand under stress; and (3) regulation of body temperature.

The reflex response to activation of one group of sensory afferents may be dependent on the input from other groups of afferents to the medullary neurons. *Several questions may be asked in this context:*

(1) What is the influence of the tonic input from certain sensory receptors on the reflex response observed when the input from one group of sensory afferents is modified? In other words, if the arterial baroreceptor input is increased or decreased, does that modify the response to chemoreceptor stimulation? (2) Can the input from cardiac vagal afferents modify the effects of changes in the activity of arterial baroreceptors or of chemoreceptors on blood pressure, renin release, antidiuretic hormone release and other variables?

These questions have physiologic implications concerning the nature of the central projections of these afferents and their neuronal connections. They are also important in pathophysiologic states where the input from arterial or cardiac receptors may be suppressed, as in hyptertension or heart failure. Under those conditions responses to activation of somatic afferents with exercise or activation of chemoreceptors with hypoxia might be drastically modified. *Three examples of important interactions are used to illustrate the concept.*

A. Carotid baroreceptors modulate the chemoreceptor and somatic reflexes: At low carotid sinus pressure, the "gains" of the chemoreceptor and somatic reflexes are augmented.

1. Carotid chemoreceptors: Elevation of carotid sinus pressure in the left carotid artery suppresses the chemoreceptor reflex activated by perfusion of the right carotid artery with hypoxic, hypercapnic blood at constant perfusion pressure (Fig. 4). Conversely, a reduction in arterial pressure induced by hemorrhage augments the vasoconstrictor response to stimulation of chemoreceptors.[21] A similar interaction occurs with respect to the hyperventilatory response to chemoreceptor stimulation, which is augmented at low carotid sinus pressure.[22]

2. Carotid somatic receptors: The reflex response to activation of the somatic reflex is also augmented during carotid sinus hypotension. Activation of somatic afferents (by contraction of skeletal muscle or by electric stimulation of the central end of the cut sciatic nerve at high frequency) causes reflex vasoconstriction in the perfused gracilis muscle, an increase in arterial pressure and tachycardia. The magnitude of this reflex response is augmented significantly when the carotid sinuses are perfused at low pressure and inhibited when the carotid sinuses are perfused at high pressure.[23] This interaction is not caused by a change in reactivity of blood vessels

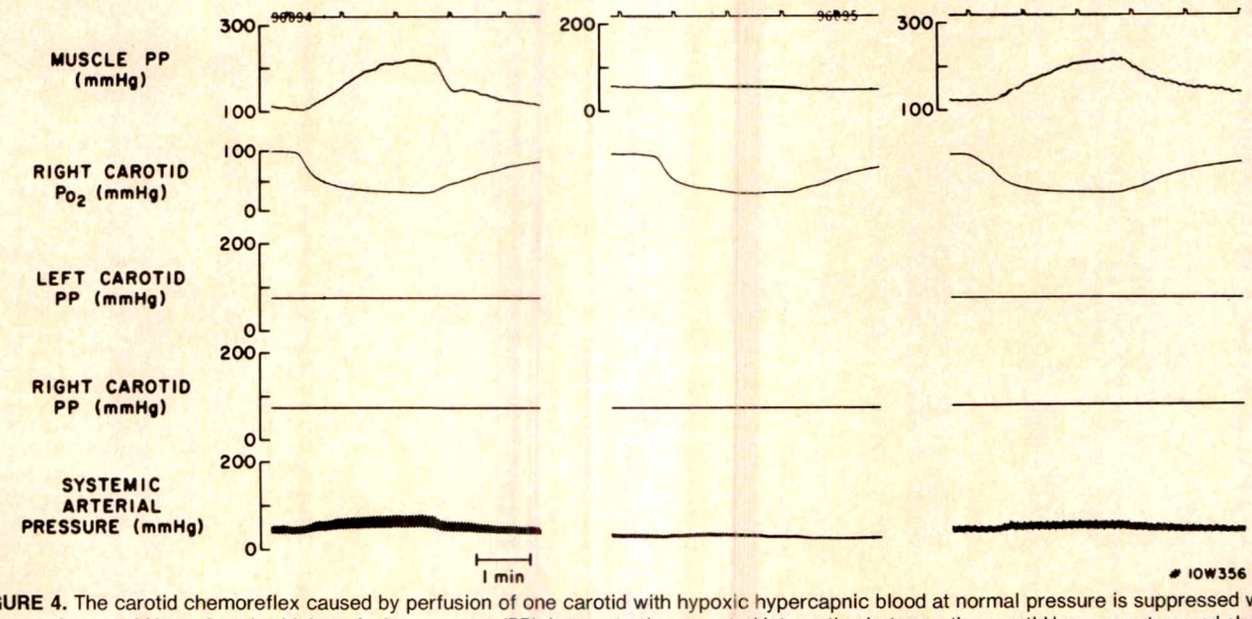

FIGURE 4. The carotid chemoreflex caused by perfusion of one carotid with hypoxic hypercapnic blood at normal pressure is suppressed when the opposite carotid is perfused at high perfusion pressure (PP) demonstrating a central interaction between the carotid baroreceptors and chemoreceptors. PO_2 = oxygen tension.

in the gracilis muscle to the released neurotransmitter, norepinephrine. When the somatic reflex is augmented at low carotid sinus pressure, the response to intraarterial norepinephrine injected into the perfused gracilis artery is, if anything, lesser than the control response and, conversely, when the somatic reflex response is inhibited at high carotid sinus pressure, the response to norepinephrine tends to be even greater. The change in gain of the somatic reflex is due to neural interactions rather than to a change in the responsiveness of vascular muscle to the released neurotransmitter.

The interaction between carotid baroreceptors and somatic afferents has clinical implications. Activation of somatic afferents in hypertensive states is associated with an increased sympathetic outflow to blood vessels. The augmented neural adrenergic response to exercise in hypertensive states may be related to the fact that carotid baroreceptor activity is suppressed in hypertension.

B. Interaction of cardiopulmonary vagal afferents with other reflexes: The cardiopulmonary vagal afferents modulate the arterial baroreceptor reflex with respect to changes in vascular resistance, antidiuretic hormone release, and renin release. They can also modulate the chemoreceptor and somatic reflexes.

1. *Cardiopulmonary arterial baroreceptors:* Carotid hypotension increases arterial pressure and vascular resistance in the gracilis muscle in dogs with cut aortic depressor nerves. Bilateral vagotomy augments this reflex.[24] It is postulated that the tonic inhibitory input from cardiopulmonary vagal afferents reduces the gain of the baroreceptor reflex, particularly in the lower range of carotid sinus pressures between 120 and 50 mm Hg.

2. *Cardiopulmonary chemoreceptors:* Similarly, the response to chemoreceptor stimulation is augmented when the vagal afferent input is absent. The reflex vasoconstrictor response to injections of nicotine or cyanide into the carotid arteries was significantly greater after than before vagotomy in animals in which the aortic depressor nerves had been cut and carotid sinus pressure was maintained constant.[24]

3. *Cardiopulmonary arterial baroreceptors and ADH:* Release of antidiuretic hormones (ADH) is under the control of both the arterial sinoaortic baroreceptors as well as the cardiopulmonary vagal afferents. Thames and Schmid[25] showed that when the aortic nerves and carotid sinus nerves are cut sequentially in the presence of the vagi, there are no changes in ADH concentration but, immediately after vagotomy, there is a significant rise. When the order of these interventions is reversed so that vagotomy is carried out first, followed by section of aortic then carotid sinus nerves, there is a progressive rise in vasopressin concentrations after section of each set of nerves. These results emphasize two points. First, that the order of interventions determines in a significant way the nature of the response, suggesting that there are interneuronal connections that modulate the final pathway for the response in a differential way. The second and more important finding is that the cardiopulmonary vagal input is critical and can suppress the influence of the arterial baroreceptors on ADH release.

4. *Cardiopulmonary somatic afferents:* The central end of the cut sciatic nerve is stimulated electrically in anesthetized dogs to activate somatic afferents and simulate exercise. The resulting decrease in renal blood flow, increase in arterial pressure and tachycardia are measured as indexes of the magnitude of the somatic reflex. During hypervolemia caused by infusion of dextran, the reflex renal response is reduced whereas, immediately after vagotomy, the response is augmented.[26] The magnitude of the renal response in these dogs with cut sinoaortic nerves is inversely related to the

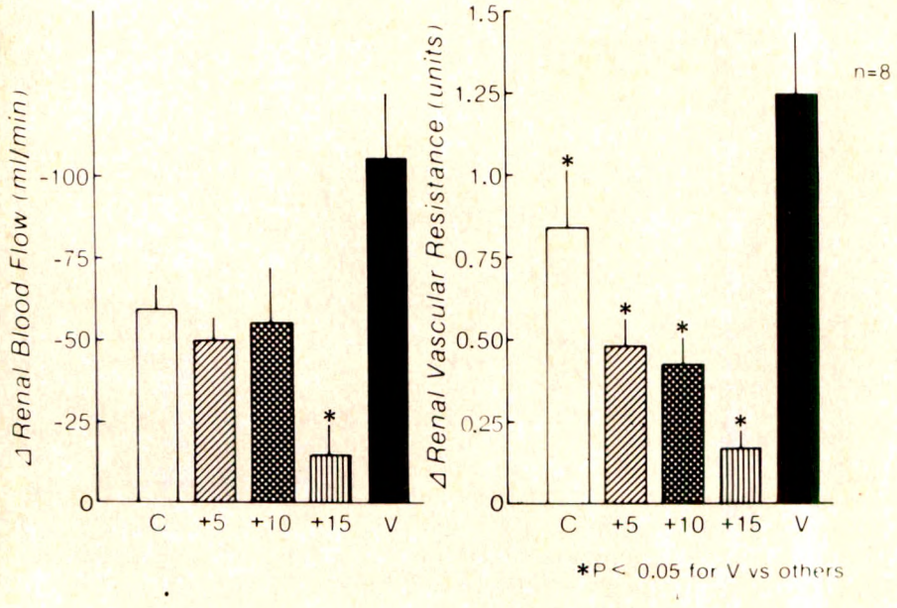

FIGURE 5. The increases in renal vascular resistance during activation of somatic afferents (**right panel**) are reduced by volume loading with intravenous dextran (5, 10 and 15 ml/kg) and augmented by vagotomy (V). A similar trend is seen for the simultaneous increase in arterial pressure and decrease in renal blood flow (**left panel**). C = control (before dextran); n = number of experiments; P = probability.

intensity of cardiopulmonary receptor activity (Fig. 5). This interaction is most evident with respect to the changes in renal vascular resistance, but it is less evident with respect to changes in arterial pressure and it is absent with respect to changes in heart rate.

In an attempt to determine whether such an interaction occurs in human beings, somatic afferents are activated by asking normal subjects to perform isometric exercise of the left arm by compressing a dynamometer. Handgrip pressures of 10 and 20 percent of maximal contraction are sustained over a period of 1.5 minutes. The resulting reflex responses are studied by measuring changes in arterial blood pressure and heart rate. This reflex response is examined in a control state and when the input from the cardiopulmonary afferent is reduced by lower body negative pressure at −5 mm Hg. Lower body negative pressure at this minimal level of suction reduces central venous pressure and causes a slight increase in forearm vascular resistance without a change in arterial pressure or heart rate. The reflex response to lower body negative pressure is ascribed to withdrawal or inhibition of cardiopulmonary baroreceptor activity. When isometric exercise is performed during this low level of lower body negative pressure, the reflex vasoconstrictor response is augmented severalfold.[27] (Fig. 6).

These findings indicate that in animals and human beings, the magnitude of reflex neuroadrenergic drive during exercise is modulated by the input from cardiopulmonary vagal afferents. It is tempting to speculate that augmented neuroadrenergic response to exercise in heart failure, which has been documented in patients as well as in animal models, might be related to the decreased afferent input from the heart. Studies by Greenberg et al.[28] and by Zucker et al.[29] demonstrated that the activity of left atrial stretch receptors with vagal afferents is suppressed in animal models of heart failure. If the large number of unmyelinated inhibitory vagal afferents from the left ventricle were hypoactive in heart failure, one might expect the augmented exercise response on the basis of the interaction we demonstrated in normal animals and human beings.

C. Interaction of thermal receptors and baroreceptors in the control of cutaneous blood flow: Thermal receptors in the skin mediate responses that modify vascular tone in cutaneous beds to either increase or decrease heat dissipation. We postulated[30] that heating of one forearm in human beings could interfere with reflex vasoconstrictor responses in the cutaneous bed (finger or hand) of the opposite arm. Lower body negative pressure at −40 mm Hg increases sympathetic efferent activity; blood flow to the fingers and forearm decreases. When one forearm is immersed in warm water, the reflex vasoconstrictor response to lower body negative pressure is markedly inhibited in the contralateral fingers but the forearm response is altered only slightly. When the temperature of the water is cooled to 10° to 12° C, the reflex response is increased. Thus, the baroreceptor reflex effect on blood flow to the fingers is inhibited when the input from thermoreceptors in the contralateral forearm signals an increase in skin temperature. This interaction does not extend as effectively to vessels of the forearm presumably because the forearm is predominantly skeletal muscle. Input from thermal receptors overrides the input from arterial or cardiopulmonary baroreceptors in the control of blood flow to the fingers.

Sensitization of Afferent Receptors

Stimulation of sensory afferent receptors may be modified by drugs or humoral factors acting on the receptor itself or on the chemical and mechanical characteristics of the tissues surrounding the receptor. Acetylstrophanthidin activates directly cardiac receptors with vagal afferents and arterial baroreceptors, causing reflex bradycardia and inhibition of sympathetic outflow. This effect is transient and lasts several minutes. We recently[31] tested the possibility that acetylstrophanthidin may sensitize cardiac inhibitory receptors and augment responses to expansion of blood volume or to myocardial ischemia. Injection of acetylstrophanthidin (25 μg) into the circumflex coronary artery of dogs with sinoaortic denervation produces an acute and transient bradycardia with decrease in sympathetic nerve activity. Ten to 15 minutes after the injection, when resting values are back to control levels, occlusion of the circumflex coronary artery causes a greater inhibition of sympathetic nerve traffic. Similarly, volume loading with infusion of dextran causes a

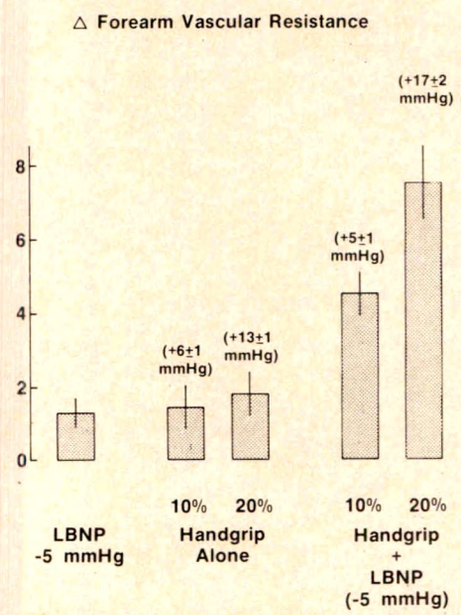

FIGURE 6. The increases in forearm vascular resistance in 11 subjects during combined lower body negative pressure (LBNP) and handgrip exercise at 10 and 20 percent of maximal voluntary contraction are much greater than those noted with handgrip exercise or lower body negative pressure alone. The **bars** represent mean changes in vascular resistance in arbitrary units (mm Hg/ml per min per 100 ml ± 1 standard error).

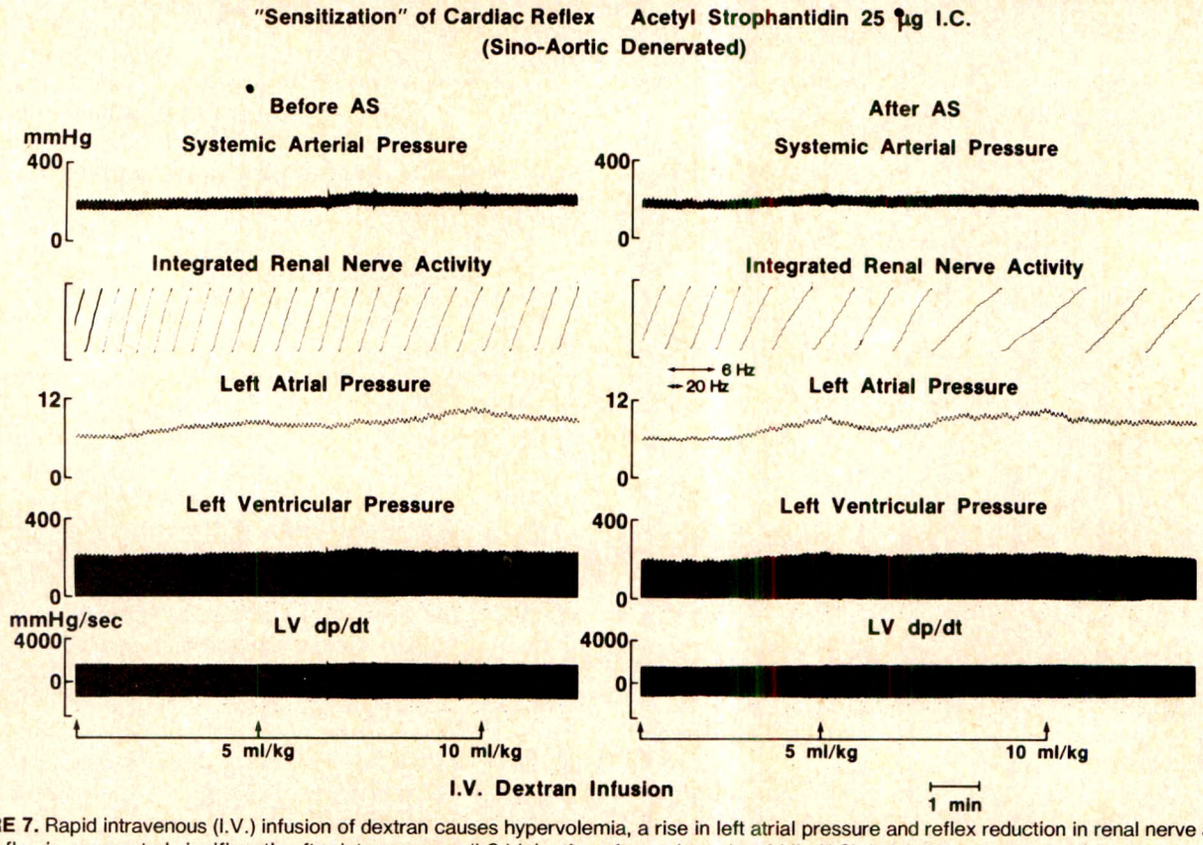

FIGURE 7. Rapid intravenous (I.V.) infusion of dextran causes hypervolemia, a rise in left atrial pressure and reflex reduction in renal nerve activity. This reflex is augmented significantly after intracoronary (I.C.) injection of acetylstrophanthidin (AS). LV dp/dt = first derivative of left ventricular pressure.

greater inhibition of renal sympathetic nerve activity after than before acetylstrophanthidin (Fig. 7).

These results suggest that one of the mechanisms of action of acetylstrophanthidin in heart failure might be to sensitize cardiac receptors and thereby result in an inhibition of sympathetic activity. In addition to its direct inotropic effect, sensitization of these baroreceptors which are known to be depressed in heart failure may explain the effect of the drug on the peripheral circulation in heart failure.

Conclusions

An overview of four important concepts related to integration of cardiovascular reflexes is presented:

1. *Nonuniformity of sympathetic efferent activity to various organs and of vagal parasympathetic efferent activity to the heart is emphasized.* The reflex control of the circulation is selective and optimal for the necessary adjustments under stress. This is evident in the differential effect on the heart and peripheral circulation in diving and during chemoreceptor stimulation. Optimal oxygen conservation and distribution are achieved by a reduction in heart rate and myocardial oxygen demand as well as coronary vasodilatation and intense peripheral vasoconstriction which limits oxygen delivery to organs that are not as dependent on oxygen as the brain and heart.

2. *Simultaneous activation of two or more sensory afferents is not uncommon in pathologic conditions.* One set of reflex responses may override the other. It is difficult to predict which reflex overrides. It appears that cardiac reflexes and reflexes related to oxygen conservation and delivery may override the baroreceptor reflexes when these are activated simultaneously.

3. *The input from the cardiopulmonary baroreceptors and the arterial baroreceptors may modify significantly responses to chemoreceptor activation and to activation of somatic afferents.* There is a significant augmentation of the somatic reflex at low carotid sinus pressures and when the cardiopulmonary vagal afferents are inhibited. The interaction between somatic and cardiopulmonary vagal afferents can be seen in man and may have implications with respect to the response to exercise in patients with hypertension as well as those with heart failure.

4. *Finally, the concept of sensitization of receptors is important.* The magnitude of a response to a specific stimulus may be modified several fold in the presence of certain drugs or hormones which alter the sensitivity of the receptors to the stimulus. The cardiopulmonary baroreceptors appear to be sensitized by acetylstrophanthidin. This sensitization may explain in part the action of digitalis on the peripheral circulation in heart failure.

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Overview of Cardiovascular Reflexes in Hypertension

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The problem of cardiovascular reflexes in hypertension poses several questions. The first is whether alterations in cardiovascular reflexes can initiate a persistent increase in arterial pressure. Another is whether it is an alteration in depressor or in pressor reflexes that matters in hypertension. Other questions concern the type and nature of the reflex alterations that actually occur in hypertension and the place of resetting of baroreflexes in the sequence of physiologic events leading to increased blood pressure.

Other articles in this Symposium provide quite extensive and detailed information on several aspects of cardiovascular reflexes in hypertension, and little can be added here, except, perhaps, a personal view, and I hope a not heavily biased one. Rather than presenting an *overview* of the problem, which presupposes a "height" of knowledge that is impossible at the present level of information, these reflections might perhaps be best characterized as an *interim* view of the problem of cardiovascular reflexes in hypertension today. It might not be the way we shall see this problem tomorrow.

There are several questions to be asked: (1) Can alterations in cardiovascular reflexes initiate a persistent rise in arterial pressure (inasmuch as hypertension is by definition a *persistent* increase in arterial pressure), or can they help maintain hypertension initiated by a nonneural mechanism (for instance, renal arterial stenosis) or contribute to maintaining an elevated sympathetic tone despite a high blood pressure? (2) Is it an alteration in depressor or in pressor reflexes that really matters in hypertension? (3) What is the nature of the reflex alterations that actually occur in hypertension?

Role of Depressor Reflexes in Initiating Hypertension

Sinoaortic reflexes: For many years, tonic control of the circulation has been thought of as almost exclusively consisting of the negative feedback exerted by depressor reflexes, mostly the sinoaortic reflexes. More recently, depressor reflexes arising from low pressure receptors in the cardiopulmonary area have been given their due share of attention.[1,2] Detailed description of the sinoaortic reflexes in the 1920s stimulated extensive research to determine whether sustained arterial hypertension could be caused by inactivation or some disturbance of the baroreceptors. These studies generated the concept of deafferentation, or debuffering or neurogenic hypertension.[3]

However, a primary role for impairment of baroreflexes in initiating hypertension has been doubted in recent years. In particular, Cowley et al.[4] have shown that the average daily increase in mean arterial

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pressure observed in dogs in which baroreflexes were interrupted by afferent denervation amounted to only a few millimeters of mercury, and that the main effect of denervation was to increase the daily variability of blood pressure values.

These conclusions are subject to some limitations. First, although the dogs studied by Cowley et al.[4] were partly vagotomized, a sufficient number of vagal fibers were spared, and it could be surmised that additional aortic receptors connected to vagal fibers[5] and depressor influences from the cardiopulmonary area[6] were still largely viable. Mancia et al.[7] in my laboratory reinvestigated the problem in cats. They found that sinoaortic denervation widened the distribution curves of mean blood pressure values (and hence considerably increased pressure variability) without causing a significant increase in the average pressure level. However, subsequent bilateral vagotomy neither increased variability further nor shifted the average blood pressure to higher values.

Brain stem connections: A different approach was used by Reis,[8] who described the pressor effects of destruction of the nucleus tractus solitarii, the brain stem relay of baroreceptor input. The pressor response is so dramatically acute in rats that these animals generally succumb to pulmonary edema.[8] In cats, the hypertension that follows the lesion acutely is not fulminating, and usually subsides in 1 or 2 days, leaving a marked variability of blood pressure.[9] However, the average increase in blood pressure, especially during daytime, was greater in cats with lesions of nucleus tractus solitarii (Fig. 1) than would have been expected from studies of dogs with sinoaortic denervation[4] or cats with combined sinoaortic and vagal denervation.[7] This more consistent hypertension might be due to the more extensive interruption of baroreceptor or depressor influences by lesions of the solitary tract nucleus. In view of the data by Mancia et al.,[7] it is unlikely that these additional depressor influences are represented by vagal fibers.

It is known that the nucleus tractus solitarii receives baroreceptor-like influences from the anterior hypothalamus,[10] and possibly from other brain areas; abolition of these influences might be responsible for the more consistent hypertension occurring after lesions of this nucleus. Furthermore, there are "depressor" or sympatho-inhibitory reflexes besides the sinoaortic and the vagal ones. Evidence has been presented[11–13] that stimulation of volume receptors connected with sympathetic afferent fibers can induce depression of sympathetic activity to the kidney. These sympathetically conducted depressor reflexes are spared in animals with sinoaortic and vagal denervation and might contribute toward preventing or hindering a permanent increase of arterial pressure in these animals. The ascending supraspinal relays of the sympathetic afferents are largely unknown; moreover, they might not involve, or might not solely involve the solitary tract nucleus, so that destruction of this nucleus might leave some of the depressor influences still unimpaired.

Long-term effects of cardiovascular deafferentation: role of renal vasoconstriction: The second question relates to the time factor; most studies of cardiovascular deafferentation extended for only relatively short periods of time after interruption of the reflexes. The long-term consequences of increased blood pressure lability induced by sinoaortic denervation have not been fully determined. Skinner et al.[14] reported persistent elevations of blood pressure for as long as 2 years in some dogs with sinoaortic denervation. More recently, Scher and Ito[15] reported that extensive sinoaortic and vagal denervation could eventually induce hypertension in dogs studied for long periods of time. Similar hints came from our observations in cats with bilateral sinoaortic denervation (Fig. 2).[16,17] Seven to 14 days after denervation, during quiet waking behavior mean arterial pressure was slightly but significantly higher than before denervation. Although moderate, this hypertension was accompanied by a marked decrease in mesenteric blood flow and, consequently, by a very marked reduction in mesenteric conductance. In two animals in which renal blood flow was also measured, similar changes were observed. Thus, interruption of sinoaortic baroreflexes could produce visceral, and presumably renal, vasoconstriction disproportionately greater than the rise in pressure. Whether this vasoconstriction, particularly the renal one, could eventually lead to more marked increases in arterial pressure and sustained hypertension is a possibility worth exploring. Long-term follow-up studies of animals after deafferentation are needed, using modern hemodynamic techniques as well as precise assessment of behavioral

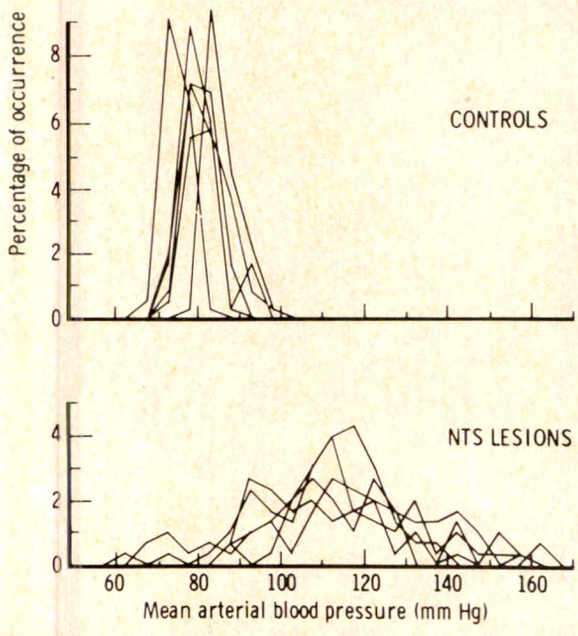

FIGURE 1. Higher values and increased lability of mean arterial pressure in five cats 1 week after creation of bilateral lesions in the nucleus tractus solitarii (NTS). (Reprinted by permission, from Nathan and Reis.[9])

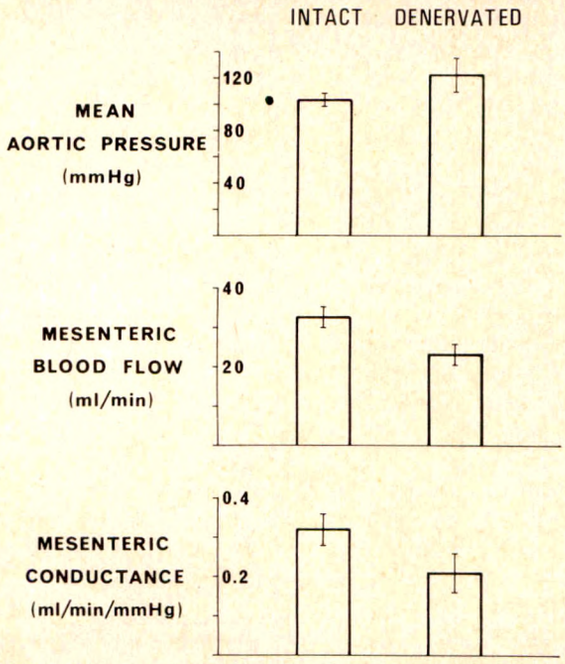

FIGURE 2. Demonstration of mesenteric vasoconstriction in six unanesthetized cats subjected to chronic (7 to 14 days) sinoaortic denervation. Measurements were made during quiet wakefulness. (Reprinted by permission, from Zanchetti et al.[17])

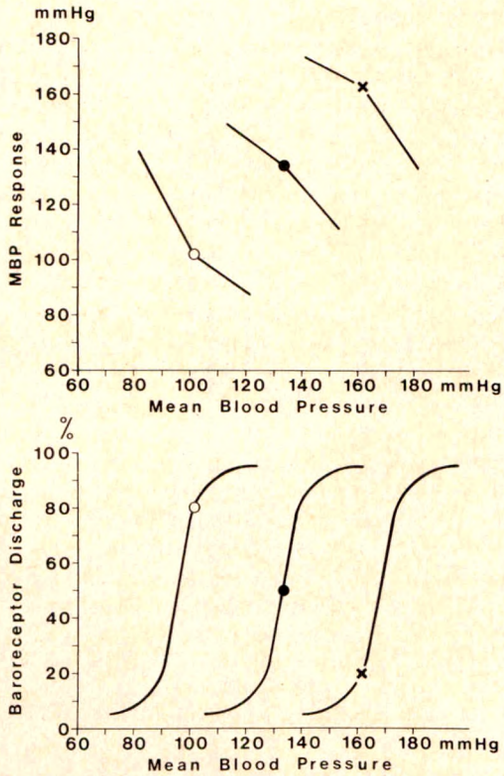

FIGURE 3. Top, changes in mean arterial blood pressure (MBP) in response to changes in carotid sinus transmural pressure in normotensive subjects (**open circle**), those with moderate hypertension (**closed circle**) and those with severe hypertension (**cross**). **Bottom,** curves represent the resetting of the carotid sinus baroreceptors in the three groups. (Modified from Mancia et al.[27])

influences and extent of deafferentation and of reinnervation.

Role of Pressor Reflexes in Initiating Hypertension

Even less is known regarding the possible role of pressor reflexes in hypertension. Coronary reflexes[18,19] are by definition phasic and might account at most for pressor reactions during anginal attacks and for the pheochromocytoma-like crisis of some patients with coronary artery disease. Even postcoronary bypass hypertension[20] has a span of existence measurable in hours only.

The validation of a more crucial role of pressor reflexes as positive feedback mechanisms in hypertension[21] *requires the previous demonstration of two conditions:* (1) that pressor responses could be induced by stimuli within the physiologic range; and (2) that these stimuli lead to sustained increases in blood pressure or to permanent hypertension. Neither of these demonstrations is available at present, but work by Malliani et al.[21] is progressing along these lines.

Alterations of Cardiovascular Reflexes in Hypertension

Baroreceptor resetting in hypertensive animals: Modifications of baroreceptor reflexes in experimental hypertension have been described under the term of resetting since publication of the paper by McCubbin et al.[22] They demonstrated upward resetting of the afferent branch of the reflex arc; more recently, Brown and his associates[23,24] presented an elegant analysis of resetting at the receptor level.

Resetting of the heart rate and the blood pressure baroreflex regulation in human hypertension: When studied in man, resetting can be defined only as resetting of the reflex response as a whole, without the possibility of analyzing changes occurring at various relays along the reflex arc. Sometimes overlooked in such studies, however, is an important distinction between heart rate[25,26] and arterial pressure[27,28] responses to baroreceptor manipulation. Although the study of either reflex response has shown a readjustment of the baroreflex in hypertension,[26,28] the pattern of readjustment indicated by heart rate responses[26] is partly different from patterns obtained by analysis of blood pressure responses.[28]

Heart rate responses can be studied by the elegant technique elaborated by Sleight and discussed in this Symposium[26]; our results with this technique confirmed his findings. However, Mancia et al.[27] described another approach to analyze not only heart rate but also reflex blood pressure responses to changes in transmural pressure across the carotid sinus (Fig. 3). The lower part of Figure 3 illustrates the type of resetting of the stimulus-response curve of the carotid sinus baroreceptors that might account for the changes in blood pressure responses observed in hypertensive patients. The change from a greater pressor reflex response and a smaller depressor reflex response typical of normotension to a smaller pressor and greater depressor reflex

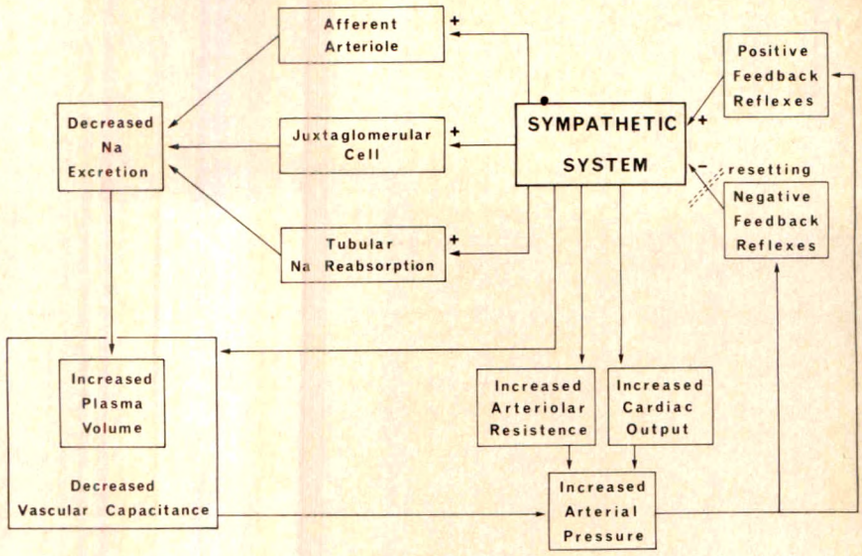

FIGURE 6. Role of sympathetic system, cardiovascular reflexes, and sympathetic control of renal function in hypertension (see text).

surprising in view of previous reports of baroreceptor afferents from renal arteries that could lower blood pressure, an effect we could never reproduce. Subsequently, Recordati et al.[46,47] demonstrated in the rat two types of previously unknown renal receptors that might be responsible for a pressor reflex. Fibers from receptors of the first type were silent at rest but discharged actively, although after a long period of latency, when the renal perfusion pressure was lowered by renal arterial occlusion[46]; they also discharged during asphyxia. Receptors of a second type[47] had a background discharge at rest, were also excited (although with a short period of latency) by decreasing renal perfusion pressure, but were particularly activated by changing the composition in tubular fluid. These receptors were activated by backflow of concentrated urine from the pelvis or of solutions with high sodium or potassium concentration, but not from the backflow of isotonic saline solution; they might represent tubular chemo- or osmotic receptors. We need more detailed information on their physiologic role.

Effects of Cardiovascular Reflexes on Renal Circulation and Functions

The kidney should be mentioned at this stage, not only as a source but also as a target of cardiovascular reflexes (Fig. 6). The effect of various cardiovascular afferents on renal circulation has been reviewed by Donald and Shepherd[1] in this Symposium. Reflex control of renin release from juxtaglomerular cells has also been recently discussed,[48] and Linden[2] has presented the evidence for control of renal excretory function by cardiovascular reflexes, a control that can be exerted both through humoral substances and through a direct neural control of tubular function.[17,49,50]

It seems particularly appropriate to mention in this Symposium those effects of cardiovascular reflexes or, more generally, of sympathetic activity on kidney function. Guyton et al.[51] stressed that pressure natriuresis is the most important or unique determinant of blood pressure in the long term. If one accepts this hypothesis unconditionally, one must then believe that increased sympathoadrenergic activity, even if sustained, can only induce short-term increases in pressure, because in the long term any pressure increase would be corrected by the volume readjustment induced through pressure natriuresis. However, all the mechanisms by which sympathetic activity can modify renal function could alter or interfere with pressure natriuresis.

The sequence of physiologic events leading to increased blood pressure does not necessarily start from the kidney (Fig. 6). It is conceivable that sympathetic activity may be primarily increased either centrally or reflexly (through a primary resetting of negative feedback reflexes or a primary increase of positive feedback reflexes); maintenance of enhanced sympathetic activity will be assured by further resetting of depressor reflexes or further increase of pressor reflexes, or both, while pressure natriuresis will be reduced through the various mechanisms of sympathetic control of renal function. Eventually, as vascular hypertrophy develops, the participation of sympathetic activity in sustaining the hypertension might become less necessary.

This is, of course, just one of the many possible sequences that could lead to elevated blood pressure and involve central and reflex sympathetic activity, the kidney, the heart and the vascular smooth muscle. Genetic factors play an important role in determining arterial pressure levels and we still must learn at which level these factors intervene; if inheritance of blood pressure is polygenic, several functions may well be involved simultaneously or differently in different persons. It remains to be more firmly established whether sympathetic activity and its reflex influences on the cardiovascular system are inherited and to what degree.

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Morphometry of Cardiac Hypertrophy Induced by Experimental Renal Hypertension

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A method for determining the mean volume of cells within a tissue has been applied to the measurement of endocardial and epicardial myocytes in the left ventricle of normal and hypertensive rats. The technique is based on nuclear counts per unit area in tissue slices of different known thicknesses. It measures the mean cell volume per nucleus and has been combined with electron microscopic morphometry. Compared with the epicardial regions, the normal endocardial regions contained 30 percent more myocytes, 27 percent less interstitial space, 48 percent less capillary volume, 17 percent less capillary surface and the same capillary length per unit of tissue volume. In terms of both the relative and absolute volumes and surface areas of their organelles, the cytoplasmic composition of normal endocardial and epicardial myocytes was nearly identical.

After 1 to 4 weeks of hypertension induced by renal arterial constriction, endocardial myocytes enlarged from 10,370 ± 410 to 12,520 ± 490 μm^3 whereas epicardial myocytes enlarged from 12,600 ± 1,600 to 17,300 ± 1,100 μm^3. The number of myocytes and the total length of capillaries remained constant. The epicardial region enlarged 37 percent with proportional increases of myocyte and interstitial volumes. In contrast, the endocardial enlargement was only 26 percent, consisting of 21 percent hypertrophy of myocytes and a 55 percent increase in interstitial components. Expansion of capillary lumens accounted for much of the interstitial enlargement throughout the myocardium. Hypertrophy of myocytes in the epicardial region was accompanied by a reduced mitochondria to myofibril ratio and disproportionately large increases (two- to three-fold) in both smooth endoplasmic reticulum and T system volume and surface area. On a cell basis the morphometric characteristics of myocytes from hypertensive rats are significantly different from normal, and significant differences occur between the inner and outer layers of the myocardium for practically every cytoplasmic component.

The ventricular wall of the mammalian heart enlarges, principally through hypertrophy of the myocytes and hyperplasia of interstitial cells, when an increased work load is imposed by various experimental conditions.[1,2] However, morphometric investigations of subcell constituents have shown only small changes in the relative cytoplasmic composition of normal and hypertrophying myocytes.[3–6] The increase in cytoplasmic constituents during hypertrophy can be fully understood only in relation to the changes in cell size or volume that are taking place. Increases in mean cell volume are not directly proportional to the augmentation in tissue volume because there may also be accompanying changes in interstitial components and cell number.

A variety of methods have been used to determine mean cell volume.[7–11] Our study uses a technique that is based on nuclear counts per unit area in tissue slices of different known thicknesses[12] and combines light and electron microscopic morphometry. The mean volume of myocytes in the endocardial and epicardial regions of rat myocardium as well as their response to 1 to 4 weeks of two kidney Goldblatt hypertension has been measured directly.

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TABLE I

Effects of 1 to 4 Weeks of Renal Hypertension*

	Normotensive Rats (no. = 9)	Hypertensive Rats (no. = 12)	*P* Value
Body weight of rats (g)	266.1 ± 8.8	203.8 ± 8.1	<0.001
Systolic blood pressure (mm Hg)	76 ± 3	173 ± 4	<0.0001
Heart weight (mg)			
Entire heart	840 ± 24	1045 ± 17	<0.001
Right ventricle	168 ± 5	172 ± 5	<0.6
Left ventricle	673 ± 23	873 ± 14	<0.001
Thickness of left mid ventricular wall (mm)	2.00 ± 0.009	2.83 ± 0.11	<0.0001

* Data are the mean values ± standard error. The probability (*P*) value was determined by Student's *t* test.

Methods

Experimental procedure: This has been described previously[13,14] and will only be summarized here. Twenty-one male Wistar Kyoto normotensive rats (Taconic Farms, Germantown, New York) weighing about 90 g each were used in this study. Hypertension was induced in 12 of these rats by constricting the left renal artery with a silver wire clip. All animals were sacrificed between the ages of 11 and 14 weeks, at which time the group with arterial constriction had been hypertensive from 1 to 4 weeks. After anesthesia with pentobarbital sodium the hearts were perfusion-fixed in diastole, excised and weighed, and the weight of the right and left ventricles including septum was recorded.

Random blocks of myocardial tissue were collected from the mid zone of the anterior wall of the left ventricle. A total of 84 blocks embedded in Araldite® were used, two from the endocardial side and two from the epicardial side of the myocardium from each control and hypertensive rat. Measurements of wall thickness were made using a magnifier with an incorporated scale. Four hundred twenty tissue slices measuring 0.96, 1.91, 2.87, 3.82 and 4.78 μm in thickness were cut with a Porter-Blum microtome (Model MT-1, Ivan Sorvall Inc., Norwalk, Connecticut) from both longitudinally and transversely oriented myofibers.

Light microscopy: The myocardial slices were examined by light microscopy at a magnification of 400 using an ocular reticle (no. 105844, Wild Herrbrugg Instruments, Inc., Farmingdale, NY) to delineate a square field on which was superimposed a uniform distribution of 42 sampling points.[15] The number of myocyte nuclei [N(n)] visible in each of five successive laterally adjacent fields, the number of sampling points overlying myocyte profiles (P_m) and the remainder of the field (P_i) were counted in the thinnest slices to determine the volume fraction [$V(c)_v$] of myocytes in the tissue. The number of myocyte profiles [N(c)] was also counted but only in the thinnest sections of transversely oriented cells. The number of binucleate myocyte profiles was counted in the thinnest sections of longitudinally oriented myocytes.

Electron microscopy: Each of the tissue blocks was further trimmed and thin-sectioned for detailed electron microscopic morphometric studies of transversely oriented myocardium at final magnifications of 6,000 and 22,200. Direct stereologic measurements of volume and surface area per unit volume and the number of profiles per unit area were calculated from the sum of all data for each rat. The standard errors of these measurements, using n equal to 9 and 12 for control and experimental animals, respectively, were then determined. An overall mean value, independent of any variation in sampling sizes, was computed from a summation of the data from all animals in each group. The tables show this overall mean ± the standard error. The significance of differences between various results was determined using Student's *t* test.

Results

Heart weight: Table I shows the mean body weights of the control and hypertensive rats at the time of sacrifice. Systolic blood pressure in hypertensive rats during the week before sacrifice showed a mean elevation of 97 mm Hg. The average heart weight was increased 24 percent and the change of 205 mg was almost

TABLE II

Volume Fraction of Myocytes [$V(c)_v$] and Number of Nuclei per 10^4 Square Micrometers of Myocyte Area [$N(n)_{A(c)}$] in Sections of Known Orientation and Thickness*

Section Thickness (μm)		Normotensive Rats		Hypertensive Rats	
		Endocardium	Epicardium	Endocardium	Epicardium
		Longitudinal Orientation			
0.96	$V(c)_v$	0.800 ± 0.012	0.718 ± 0.023	0.800 ± 0.021	0.747 ± 0.017
	$N(n)_{A(c)}$	3.64 ± 0.30	3.28 ± 0.21	2.51 ± 0.14	1.80 ± 0.12
1.91	$N(n)_{A(c)}$	4.34 ± 0.33	3.74 ± 0.22	3.29 ± 0.15	2.38 ± 0.11
2.87	$N(n)_{A(c)}$	5.25 ± 0.44	4.69 ± 0.20	4.08 ± 0.13	3.03 ± 0.16
3.82	$N(n)_{A(c)}$	6.11 ± 0.46	5.22 ± 0.16	4.73 ± 0.12	3.53 ± 0.16
4.78	$N(n)_{A(c)}$	7.35 ± 0.40	6.58 ± 0.15	5.65 ± 0.22	4.16 ± 0.13
		Transverse Orientation			
0.96	$V(c)_v$	0.765 ± 0.013	0.692 ± 0.019	0.772 ± 0.012	0.754 ± 0.009
	$N(n)_{A(c)}$	8.01 ± 0.43	9.16 ± 0.30	6.79 ± 0.28	6.52 ± 0.91
1.91	$N(n)_{A(c)}$	8.69 ± 0.49	9.51 ± 0.30	7.63 ± 0.46	7.22 ± 0.46
2.87	$N(n)_{A(c)}$	9.94 ± 0.50	10.85 ± 0.53	8.69 ± 0.47	8.06 ± 0.37
3.82	$N(n)_{A(c)}$	10.67 ± 0.42	11.48 ± 0.34	9.24 ± 0.55	8.31 ± 0.34
4.78	$N(n)_{A(c)}$	11.72 ± 0.35	11.50 ± 0.60	9.98 ± 0.62	8.65 ± 0.37

* Data are the mean values ± standard error.

response in hypertension could be explained by a shift of the baroreceptor stimulus-response curve to the right and a progressive shift of the set-point of the reflex from the upper to the lower part of the sigmoid curve. This implies not only that the threshold of the carotid sinus baroreflex has been increased by hypertension, but also that its sensitivity has remained substantially unchanged. The sensitivity of the reflex in hypertensive subjects is better assessed by measuring depressor responses, whereas in normotensive subjects pressor responses are the better index of sensitivity. The increase in threshold certainly fits with the baroreflex resetting suggested by studies of heart rate responses, but the unchanged sensitivity does not.

Interpretation of differences between resetting of heart rate and blood pressure responses: Various interpretations of the differences between resetting of the blood pressure and heart rate baroreflex are possible. The *first* takes into consideration the possible influences of the initial response on the final outcome of the reflex. Reflex heart rate responses to pressor and depressor drugs can be analyzed as part of an open loop system, where the response itself does not influence the baroreceptors significantly, whereas the reflex blood pressure responses are necessarily part of a closed loop system, in which the response directly affects baroreceptors of the area being tested as well as of companion reflexogenic areas.[29] Although this is an important argument, it is unlikely that it explains the differences entirely. Simultaneous involvement of aortic baroreceptors in the closed loop system could hardly obscure a loss of sensitivity of the reflex and explain the shift of the set-point from the upper to the lower portion of the baroreceptor stimulus-response curve in hypertensive patients.

The second interpretation suggests that the heart rate and blood pressure are predominantly controlled through different reflexogenic areas: heart rate predominantly by the aorta, blood pressure predominantly by the carotid sinus.[30] This interpretation is supported by the changes in heart rate in different phases of the Valsalva maneuver.[31] The rise in arterial pressure that occurs at the very beginning of the maneuver, when the intrathoracic pressure is suddenly increased, is not generally accompanied by bradycardia, whereas the overshoot increase in pressure after release of intrathoracic pressure is accompanied by intense bradycardia. This difference in response is probably related to the difference in baroreceptors involved; in phase I, there is no increase in aortic transmural pressure because the increase in intraaortic pressure is balanced by the increase in intrathoracic pressure; consequently, the aortic baroreceptors are not stimulated and only the carotid baroreceptors are activated. In contrast, with the post-release overshoot (phase IV), intense stimulation of the carotid sinus receptors, and bradycardia ensues. This interpretation implies that aortic receptors are more rapidly or more profoundly altered in hypertension than are the carotid sinus receptors. Although there is admittedly no evidence for this, a possible

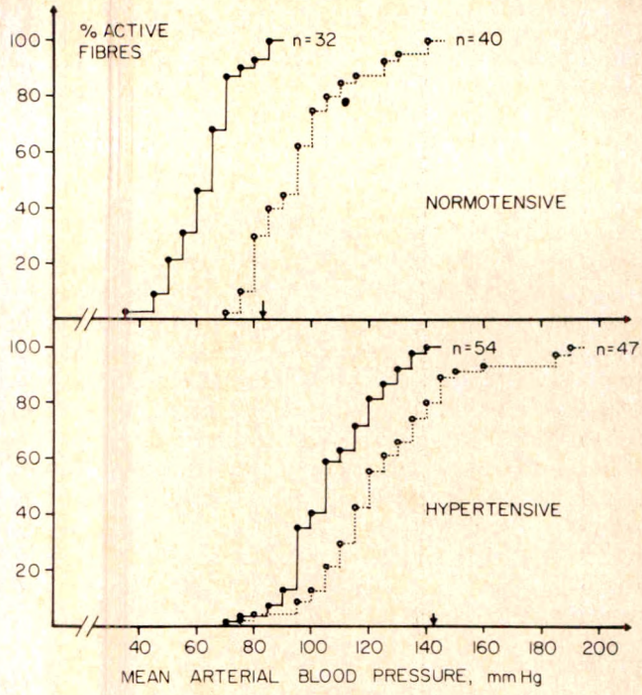

FIGURE 4. Activation of medullated (**continuous lines**) and nonmedullated (**dotted lines**) aortic baroreceptor fibers in normotensive (**top**) and renal hypertensive rabbits (**bottom**). In the hypertensive animals activation of both types of fibers occurs at higher pressure values, but the relative increase in threshold is greater for medullated than for nonmedullated fibers. n = number of fibers. (Reprinted by permission, from Jones and Thoren.[32])

structural basis for an earlier or greater alteration of aortic than carotid sinus receptors could be sought in the contrast between the thick aortic wall and the thin, highly distensible carotid sinus. These differences in wall characteristics might be associated with differences in receptor structure and excitability.

A third interpretation is that different sets of baroreceptors at various sites are specialized in controlling predominantly either heart rate or blood pressure, and that those controlling the heart rate lose their sensitivity to a greater extent in hypertension. For instance, Brown et al.[23] showed that in the aortic nerve of the rat myelinated fibers have a greater sensitivity to discharge for frequencies near the heart rate, and that they provide a better feedback to the central nervous system with respect to heart rate information than do unmyelinated fibers. Although both myelinated and unmyelinated baroreceptor fibers have been found to be reset in hypertensive animals,[23,32] data from Jones and Thoren[32] suggest that unmyelinated receptors are less reset than are myelinated receptors (Fig. 4).

In yet another explanation, it is conceivable that differences in heart rate and blood pressure responses are due to different central readjustments of the reflex paths subserving these two responses. That the baroreflex can be influenced by central mechanisms is well recognized[33]; Hilton[34] demonstrated hypothalamic inhibition of the bradycardia elicited by baroreflex stimulation. This hypothalamic influence on the baro-

reflex appeared limited to the heart rate component and did not extend to the peripheral vessel response,[35] a finding that would fit very well in the framework of this interpretation.

A fifth hypothesis suggests that the difference in readjustment of heart rate and blood pressure responses to the baroreflex lies in the different alteration of the peripheral effector structure in hypertension. Folkow[36] has stressed that the increased wall to lumen ratio in hypertrophied arterioles would amplify the effect of vasoconstrictive stimuli; it is not inconceivable therefore that even a small decrease in sympathetic activity in response to stimulation of a reset baroreflex might cause a greater vascular dilatation and thus mask or compensate for the loss of receptor responsiveness.

In light of these various interpretations, it is important to stress that the concepts we derived[28] from the stimulus-blood pressure response curve of the carotid sinus reflex agree with the concept advanced in previous studies of heart rate response,[26] while placing it on firmer grounds in relation to regulation of blood pressure. In the final analysis, baroreflex resetting in hypertension implies two consequences[28]: (1) in spite of the higher resting blood pressure, there is less baroreceptor activity to be inhibited by carotid sinus inactivation (and hence a smaller blood pressure increase follows any decrease in sinus activity); but (2) as a consequence of this smaller tonic inhibition, a rather high level of sympathetic activity could persist and play an important role in maintenance of arterial pressure.

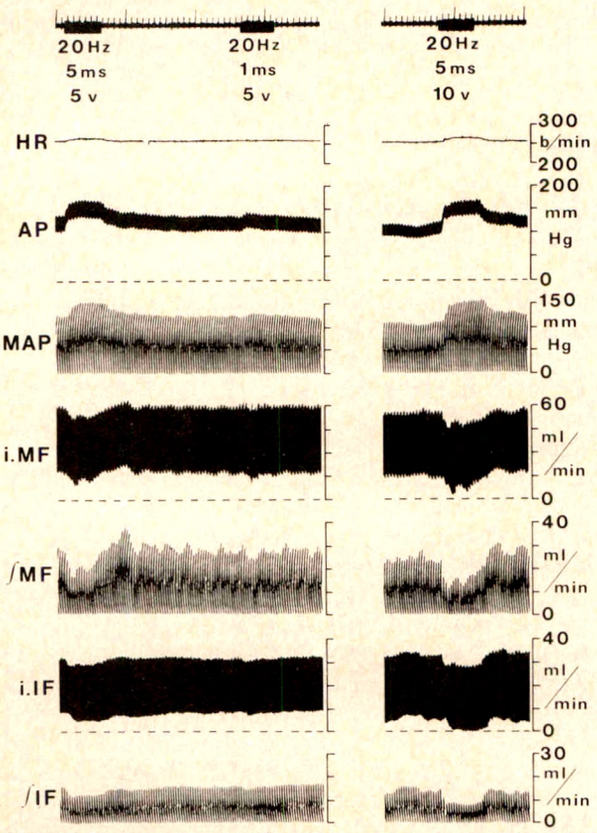

FIGURE 5. Increase in arterial pressure and in mesenteric and iliac vasoconstriction during stimulation of afferent fibers in the left renal nerve with different stimuli variables. **From the top down:** time in 5 second and 1 minute intervals, and stimulus marker; heart rate (HR); aortic pressure (AP); mean (integrated) aortic pressure (MAP); instaneous superior mesenteric blood flow (i.MF); mean (integrated) superior mesenteric blood flow ($\int$MF); instantaneous left external iliac blood flow (i.IF); mean (integrated) left external iliac blood flow ($\int$IF). b = beats; ms = milliseconds. (Reprinted by permission, from Calaresu et al.[45])

Secondary versus primary baroreflex resetting in hypertension: Is baroreflex resetting necessarily secondary to the rise in pressure, or may it be primary, that is, antedating hypertension and possibly causing it? That secondary resetting occurs has been abundantly proved since the time of the first experiments of McCubbin et al.[21] In man, we have recently found that resetting of the carotid sinus reflex is the same in patients with renovascular hypertension as it is in patients with essential hypertension.[37]

In contrast, evidence for a primary baroreflex reset is lacking. In this context, it is interesting that Andresen et al.[24] have stressed that while baroreceptor resetting is associated with reduced aortic distensibility and possibly dependent on it in rats or rabbits with renal hypertension, this is not the case for spontaneously hypertensive rats. In the latter, aortic distensibility is still normal at an age (10 weeks) at which resetting and decreased sensitivity of the aortic receptors already occur. Therefore, in the spontaneously hypertensive rat resetting could be at least partly ascribed to primary changes in the receptors. Some experimental evidence[38] was even advanced suggesting that these changes might consist in a reduction of the sodium to potassium permeability ratio in the receptor membrane, although the sodium concentrations used were apparently beyond the physiologic range.

Many investigators have reported significant disturbances in membrane permeability and transport of sodium and potassium in vascular smooth muscle[39] and red blood cells of spontaneously hypertensive rats.[40–42] Similar alterations were also reported in the red blood cells or lymphocytes of hypertensive patients.[43,44] It is tempting to assume some hypothetical link between these disturbances and alterations in baroreceptors; it could be surmised, although only as a working hypothesis, that primary changes in baroreceptors might be produced genetically in the spontaneously hypertensive rat and perhaps in essential hypertension in human beings.

Reflexes Arising From the Kidney and Blood Pressure Regulation

An overview of cardiovascular reflex regulation in hypertension is not complete without mention of the information obtained from renal studies. Calaresu et al.[45] in this laboratory showed that electrical stimulation of afferent renal nerves induced a rise in arterial pressure associated with diffuse visceral and muscular vasoconstriction (Fig. 5). This finding was somewhat

completely caused by a 30 percent increase in left ventricular weight. The average thickness of the mid zone of the anterior wall of the left ventricle was 42 percent greater in hypertensive rats.

Number of myocyte nuclei: A total of 48,528 myocyte nuclei were counted in 3,142 microscopic fields in the sampling of five different section thicknesses, at two mutually perpendicular orientations, in two tissue regions and in both groups of animals. Figures calculated from these data are shown in Table II. The volume fraction of myocytes in the myocardium $[V(c)_v]$ was obtained from the relation: $V(c)_v = P_m/(P_m + P_i)$.

The number of myocyte nuclei per 10^4 μm^2 cross-sectional area of myocytes $[N(n)_{A(c)}]$ was then calculated using the equation: $N(n)_{A(c)} = N(n)_A/V(c)_v = N(n)/A_M$ $(P_m + P_i)/P_m\ 10^2$, where A_M is the total area of myocardium sampled in square millimeters. An overall unweighted mean value of $N(n)_{A(c)}$ was determined from the summed data from all animals in each group for each slice thickness.

When the number of nuclei per unit area $[N(n)_{A(c)}]$ is plotted as a function of section thickness, it produces a straight line with a slope equal to $[V(c)_n]$, the mean myocyte volume per myocyte nucleus ($\mu m^3 \times 10^{-4}$).[13] Figure 1 contains graphs of the mean ± standard error values for the four sets of endocardial and epicardial data shown in Table II. Regression lines drawn in these graphs were calulated on the mean values[16] and their slopes and standard errors (no. = 5) are listed in Table III. A t test applied to the paired independent determinations of $V(c)_n$ showed highly significant agreement in all four sets of measurements. Therefore, the duplicate estimations were averaged to give the mean myocyte volumes (per nucleus) and overall standard errors (n = 10) shown in Table III.

Mean cell volume of ventricular myocytes: The mean cell volume per nucleus is strictly equivalent to mean cell volume only in mononucleate cell populations. Because bi- and multinucleate myocytes do exist in the myocardium, their frequency was evaluated by recording the number of binucleate cell profiles in a sampling of all of the thinnest longitudinally oriented myocardial sections (Table IV). The data in Table IV imply approximately 2 to 3 percent binucleate cells among the myocytes of control myocardium and approximately 4 percent among those of hypertensive rats. The mean cell volumes of ventricular myocytes listed in Table IV were obtained by increasing the measured cell volumes per nucleus (Table III) by the corresponding estimated percentages of binucleate cells in

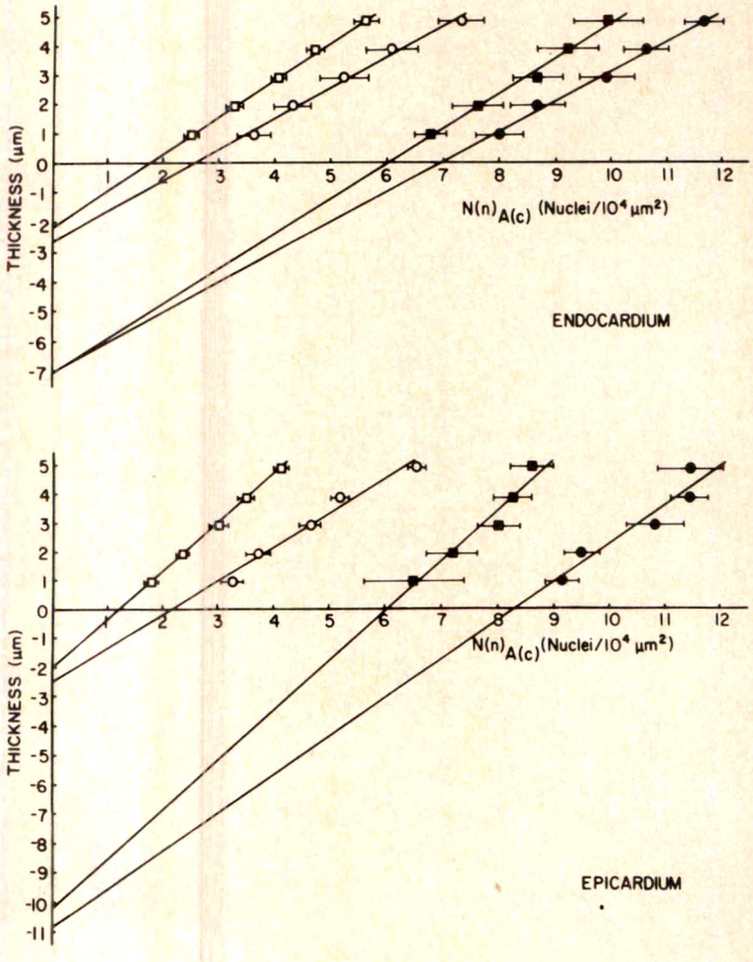

FIGURE 1. Graphs of the data presented in Table II. **Circles** represent normotensive data and squares represent measurements from hypertensive rats. **Open circles** and **squares** (○, □) show the observations from longitudinally oriented myofibers, and **solid circles** and **squares** (●, ■) show the corresponding results from transversely oriented myofibers. In the endocardial region of the left ventricle (**top**) the hypertrophied myocytes of hypertensive rats (**squares**) yield regression lines with a steeper slope. Duplicate measurements at mutually perpendicular tissue orientations (**open versus solid**) show reproducibility in their nearly parallel lines. Similar comparisons are evident in the epicardial region (**bottom**) where the normally larger cells have greater slopes and the increase in slope due to cellular hypertrophy is more marked. $N(n)_{A(c)}$ = the number of nuclei per unit area.

TABLE III

Cell Volume Per Nucleus (μm^3) of Left Ventricular Myocytes Determined From Longitudinally and Transversely Oriented Sections*

	Normotensive Rats		Hypertensive Rats	
	Endocardium	Epicardium	Endocardium	Epicardium
Longitudinal orientation	10,270 ± 630	11,500 ± 2,200	12,350 ± 320	16,260 ± 310
Transverse orientation	10,090 ± 490	13,100 ± 2,300	11,750 ± 890	17,000 ± 2,200
P value	<0.9	<0.7	<0.6	<0.8
Average of both orientations	10,180 ± 400	12,300 ± 1,600	12,050 ± 470	16,600 ± 1,100

* Data are the mean value ± standard error.
P = probablility.

TABLE IV

Mean Cell Volume of Left Ventricular Myocytes Based on Estimated Percent of Binucleate Cells

	Normotensive Rats		Hypertensive Rats	
	Endocardium	Epicardium	Endocardium	Epicardium
Area of myocardium sampled (mm^2)	3.429	3.466	3.174	6.566
no. of mononucleate cells	971.0	784.0	601.0	829.0
no. of binucleate cells	14.0	16.0	18.0	27.0
Percent of binucleate cell profiles	1.4	2.0	2.9	3.2
Estimated percent of binucleate cells	1.9	2.7	3.9	4.3
Cell volume/myocyte (μm^3)	10,370 ± 410*	12,600 ± 1,600	12,520 ± 490	17,300 ± 1,100

* Data are the mean value ± standard error.

TABLE V

Composition of Left Ventricular Myocardium*

	Normotensive Rats	Hypertensive Rats	*P* Value
Volume percent of myocardium interstitium			
Endocardial†	15.1 ± 1.3	18.6 ± 1.3	<0.05
Epicardial	20.6 ± 1.7	20.2 ± 1.0	<0.7
P	<0.025	<0.6	
Myocytes			
Endocardial	84.9 ± 1.3	81.4 ± 1.3	<0.05
Epicardial	79.4 ± 1.7	79.8 ± 1.0	<0.7
P	<0.025	<0.6	
Volume percent of myocytes			
Nucleus			
Endocardial	1.08 ± 0.22	0.78 ± 0.14	<0.3
Epicardial	1.12 ± 0.21	0.80 ± 0.14	<0.3
P	<0.9	<0.95	
Cytoplasm			
Endocardial	98.92 ± 0.22	99.22 ± 0.14	<0.3
Epicardial	98.88 ± 0.21	99.20 ± 0.14	<0.3
P	<0.9	<0.95	
no. of profiles			
Myocytes			
Endocardial	447	583	
Epicardial	829	548	
Myocyte nuclei			
Endocardial	60	84	
Epicardial	104	82	

* Data are mean values ± standard error.
† Endocardial and epicardial regions of the left ventricular myocardium.
P = probability.

each population.[13] Epicardial myocytes were larger than endocardial myocytes and hypertension produced a significant hypertrophy of 37 and 21 percent, respectively, in these cells.

Relative volumes of endocardial and epicardial myocardium: The volume composition of myocardium (Table V) was significantly different in endocardial and epicardial regions in control rats. Hypertension induced a significant change in the relative volumes of endocardial components but not in those of the epicardium. The nuclear volume fraction within myocytes were consistently lower in the experimental group, indicating a decreased nucleus to cytoplasm ratio.

Volume relation of the cytoplasmic constituents of myocytes (Table VI): Although no significant differences were found in comparing the relative volumes of subcell fractions between endocardial and epicardial cells in the control rats, the same comparison in hypertensive rats showed significant variations in the myofibrillar and smooth endoplasmic reticulum (SER) fractions. Hypertension produced significant alterations in the myofibrillar, mitochondrial and smooth endoplasmic reticular components of endocardial myocytes and in the mitochondrial, smooth endoplasmic reticulum and T system fractions of epicardial myocytes. The mitochondria to myofibril ratio, an index frequently used to characterize hypertrophic changes in the myocardium, was significantly reduced only in endocardial cells. However, the volume ratio of smooth endoplasmic reticulum to myofibrils showed a significant elevation in both the endocardium and epicardium. Measurements of the number and area of mitochondrial profiles indicated that their mean cross-sectional area is larger

TABLE VI

Subcell Characterization of Myocytes: Volume Relations*

	Normotensive Rats	Hypertensive Rats	*P* Value
Volume percent			
Myofibrils			
Endocardial†	53.8 ± 1.1	57.0 ± 0.6	<0.02
Epicardial	54.5 ± 0.6	55.1 ± 0.6	<0.7
P value	<0.7	<0.05	
Mitochondria			
Endocardial	33.8 ± 0.9	30.4 ± 0.4	<0.005
Epicardial	32.9 ± 0.3	31.0 ± 0.4	<0.025
P value	<0.4	<0.5	
Smooth endoplasmic reticulum (SER)			
Endocardial	4.9 ± 0.2	5.9 ± 0.1	<0.005
Epicardial	4.9 ± 0.2	6.8 ± 0.2	<0.001
P value	<1.0	<0.005	
T system			
Endocardial	0.9 ± 0.1	1.2 ± 0.1	<0.2
Epicardial	0.9 ± 0.1	1.3 ± 0.1	<0.005
P value	<1.0	<0.5	
Matrix			
Endocardial	6.6 ± 0.5	5.5 ± 0.4	<0.2
Epicardial	6.8 ± 0.4	5.8 ± 0.4	<0.2
P value	<0.98	<0.6	
Mitochondrial volume/myofibrillar volume			
Endocardial	0.627 ± 0.030	0.534 ± 0.011	<0.01
Epicardial	0.602 ± 0.012	0.563 ± 0.016	<0.1
P value	<0.5	<0.2	
Smooth endoplasmic reticulum volume/myofibrillar volume			
Endocardial	0.0906 ± 0.0039	0.1035 ± 0.0026	<0.02
Epicardial	0.0889 ± 0.0034	0.1233 ± 0.0042	<0.001
P value	<0.8	<0.001	
Mitochondrial profiles (cytoplasmic area, μm^2)			
Endocardial	12796 (7382)	14207 (8739)	
Epicardial	10049 (6414)	13189 (9020)	
Transverse cross-sectional area/mitochondrion (μm^2)			
Endocardial	0.195 ± 0.015	0.187 ± 0.006	<0.7
Epicardial	0.210 ± 0.007	0.212 ± 0.007	<0.9
P value	<0.5	<0.02	

* Data are mean values ± standard error.
† Endocardial and epicardial regions of left ventricular myocardium.

in epicardial than in endocardial cells but is not changed in hypertension.

Membrane surface relations in the four groups of myocytes are given in Table VII. No significant differences were found in comparing endocardial and epicardial cells. Hypertension caused some increase in the relative surface area of smooth endoplasmic reticulum and T system membranes with respect to cytoplasmic volumes.

Mean transverse cross-sectional areas of myocyte profiles (Table VIII): These were calculated from the data in Table V. The numbers of myocytes per cubic millimeter of myocardium were derived from their measured mean volumes and volume fractions. Distinct

TABLE VII

Subcell Characterization of Myocytes: Membrane Surface Relations*

	Normotensive Rats	Hypertensive Rats	*P* Value
Square micrometers mitochondrial envelope/μm^3 cytoplasm			
Endocardial	3.26 ± 0.13	3.22 ± 0.09	<0.8
Epicardial	2.97 ± 0.06	3.01 ± 0.10	<0.8
P value	<0.1	<0.1	
Square micrometers smooth endoplasmic reticulum/μm^3 cytoplasm			
Endocardial	0.930 ± 0.053	1.18 ± 0.07	<0.2
Epicardial	0.894 ± 0.047	1.25 ± 0.04	<0.001
P value	<0.7	<0.5	
Square micrometers T system/μm^3 cytoplasm			
Endocardial	0.203 ± 0.017	0.270 ± 0.018	<0.025
Epicardial	0.209 ± 0.031	0.274 ± 0.018	<0.1
P value	<0.9	<0.9	

* Data are the mean values ± standard error.
P = probability.

differences between the inner and outer regions of the ventricular wall indicate a transmural gradient of cellularity. If we assume that this gradient is linear, then the average concentration of myocytes in the left ventricle of control rats would be 72,500 cells/mm.[3] The average left ventricular weight in the control rats was 673 ± 23 mg, which, with the assumption of a tissue density equal to 1.06 mg/μm^3,[17] implies a total of 46.0 ± 3.3 million myocytes in the left ventricle of the rat. A parallel calculation of myocyte number in the hypertrophied ventricle weighing 873 ± 14 mg is 45.8 ± 1.9 million cells. Thus, there is no indication of significant hyperplasia of ventricular myocytes in hypertension.

Cell and interstitial volumes: The availability of measured cell volumes allows the quantitative characterization of the subcell constituents of myocytes in

TABLE VIII

Mean Characteristics of Endocardial and Epicardial Myocytes in Left Ventricular Myocardium*

	Normotensive Rats	Hypertensive Rats	*P* Value
Volume (μm^3)			
Endocardial†	10,370 ± 410	12,520 ± 490 (21)‡	<0.01
Epicardial	12,600 ± 1,600	17,300 ± 1,100 (37)	<0.05
P value	<0.3	<0.005	
Transverse cross-sectional area (μm^2)			
Endocardial	155 ± 8	198 ± 6 (28)	<0.001
Epicardial	122 ± 9	204 ± 18 (67)	<0.005
P value	<0.02	<0.8	
no./mm^3 myocardium × 10^{-3}			
Endocardial	81.9 ± 3.5	65.0 ± 2.8 (−21)	<0.005
Epicardial	63.0 ± 8.5	46.1 ± 3.2 (−37)	<0.2
P value	<0.1	<0.001	
Constituent volumes (μm^3):			
Nucleus			
Endocardial	112 ± 23	98 ± 18 (−13)	<0.7
Epicardial	141 ± 32	138 ± 26 (−2)	<0.9
P value	<0.5	<0.3	
Myofibrils			
Endocardial	5,520 ± 240	7,080 ± 290 (28)	<0.005
Epicardial	6,790 ± 900	9,460 ± 640 (39)	<0.05
P value	<0.3	<0.005	
Mitochondria			
Endocardial	3,470 ± 140	3,780 ± 160 (9)	<0.3
Epicardial	4,100 ± 540	5,320 ± 380 (30)	<0.2
P value	<0.4	<0.005	
Smooth endoplasmic reticulum			
Endocardial	503 ± 31	733 ± 31 (46)	<0.001
Epicardial	610 ± 82	1,170 ± 83 (92)	<0.001
P value	<0.3	<0.001	
T system			
Endocardial	92 ± 12	149 ± 14 (62)	<0.02
Epicardial	112 ± 19	223 ± 23 (99)	<0.005
P value	<0.5	<0.02	
Matrix			
Endocardial	677 ± 52	683 ± 54 (1)	<1.0
Epicardial	850 ± 110	995 ± 95 (17)	<0.4
P value	<0.3	<0.02	
Surface areas (μm^2):			
Mitochondrial envelope			
Endocardial	33,400 ± 1,800	40,000 ± 2,000 (20)	<0.1
Epicardial	37,000 ± 4,900	51,700 ± 3,900 (40)	<0.7
P value	<0.6	<0.02	
Smooth endoplasmic reticulum			
Endocardial	9,540 ± 660	14,700 ± 1,000 (54)	<0.005
Epicardial	11,100 ± 1,500	21,500 ± 1,600 (94)	<0.001
P value	<0.5	<0.005	
T system			
Endocardial	2,080 ± 190	3,350 ± 260 (61)	<0.001
Epicardial	2,600 ± 520	4,700 ± 440 (81)	<0.02
P value	<0.4	<0.02	
Sarcolemma			
Endocardial	3,770 ± 240	4,670 ± 260 (24)	<0.05
Epicardial	5,360 ± 770	5,540 ± 480 (3)	<0.95
P value	<0.01	<0.2	
Sarcolemma and T system			
Endocardial	5,850 ± 320	8,020 ± 360 (37)	<0.002
Epicardial	7,960 ± 920	10,240 ± 650 (29)	<0.1
P value	<0.1	<0.02	

* Data are the mean values ± standard error.
† Epicardial and endocardial regions of left ventricular myocardium.
‡ The percent increase produced by hypertension.
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* Data are the mean values ± standard error.
P = probability.

differences between the inner and outer regions of the ventricular wall indicate a transmural gradient of cellularity. If we assume that this gradient is linear, then the average concentration of myocytes in the left ventricle of control rats would be 72,500 cells/mm.^{3} The average left ventricular weight in the control rats was 673 ± 23 mg, which, with the assumption of a tissue density equal to 1.06 mg/μm^3,[17] implies a total of 46.0 ± 3.3 million myocytes in the left ventricle of the rat. A parallel calculation of myocyte number in the hypertrophied ventricle weighing 873 ± 14 mg is 45.8 ± 1.9 million cells. Thus, there is no indication of significant hyperplasia of ventricular myocytes in hypertension.

Cell and interstitial volumes: The availability of measured cell volumes allows the quantitative characterization of the subcell constituents of myocytes in

TABLE VIII

Mean Characteristics of Endocardial and Epicardial Myocytes in Left Ventricular Myocardium*

	Normotensive Rats	Hypertensive Rats	*P* Value
Volume (μm^3)			
Endocardial†	10,370 ± 410	12,520 ± 490 (21)‡	<0.01
Epicardial	12,600 ± 1,600	17,300 ± 1,100 (37)	<0.05
P value	<0.3	<0.005	
Transverse cross-sectional area (μm^2)			
Endocardial	155 ± 8	198 ± 6 (28)	<0.001
Epicardial	122 ± 9	204 ± 18 (67)	<0.005
P value	<0.02	<0.8	
no./mm^3 myocardium × 10^{-3}			
Endocardial	81.9 ± 3.5	65.0 ± 2.8 (−21)	<0.005
Epicardial	63.0 ± 8.5	46.1 ± 3.2 (−37)	<0.2
P value	<0.1	<0.001	
Constituent volumes (μm^3):			
Nucleus			
Endocardial	112 ± 23	98 ± 18 (−13)	<0.7
Epicardial	141 ± 32	138 ± 26 (−2)	<0.9
P value	<0.5	<0.3	
Myofibrils			
Endocardial	5,520 ± 240	7,080 ± 290 (28)	<0.005
Epicardial	6,790 ± 900	9,460 ± 640 (39)	<0.05
P value	<0.3	<0.005	
Mitochondria			
Endocardial	3,470 ± 140	3,780 ± 160 (9)	<0.3
Epicardial	4,100 ± 540	5,320 ± 380 (30)	<0.2
P value	<0.4	<0.005	
Smooth endoplasmic reticulum			
Endocardial	503 ± 31	733 ± 31 (46)	<0.001
Epicardial	610 ± 82	1,170 ± 83 (92)	<0.001
P value	<0.3	<0.001	
T system			
Endocardial	92 ± 12	149 ± 14 (62)	<0.02
Epicardial	112 ± 19	223 ± 23 (99)	<0.005
P value	<0.5	<0.02	
Matrix			
Endocardial	677 ± 52	683 ± 54 (1)	<1.0
Epicardial	850 ± 110	995 ± 95 (17)	<0.4
P value	<0.3	<0.02	
Surface areas (μm^2):			
Mitochondrial envelope			
Endocardial	33,400 ± 1,800	40,000 ± 2,000 (20)	<0.1
Epicardial	37,000 ± 4,900	51,700 ± 3,900 (40)	<0.7
P value	<0.6	<0.02	
Smooth endoplasmic reticulum			
Endocardial	9,540 ± 660	14,700 ± 1,000 (54)	<0.005
Epicardial	11,100 ± 1,500	21,500 ± 1,600 (94)	<0.001
P value	<0.5	<0.005	
T system			
Endocardial	2,080 ± 190	3,350 ± 260 (61)	<0.001
Epicardial	2,600 ± 520	4,700 ± 440 (81)	<0.02
P value	<0.4	<0.02	
Sarcolemma			
Endocardial	3,770 ± 240	4,670 ± 260 (24)	<0.05
Epicardial	5,360 ± 770	5,540 ± 480 (3)	<0.95
P value	<0.01	<0.2	
Sarcolemma and T system			
Endocardial	5,850 ± 320	8,020 ± 360 (37)	<0.002
Epicardial	7,960 ± 920	10,240 ± 650 (29)	<0.1
P value	<0.1	<0.02	

* Data are the mean values ± standard error.
† Epicardial and endocardial regions of left ventricular myocardium.
‡ The percent increase produced by hypertension.
P = probability.

terms of absolute measurements per cell. These figures (Table VIII) are the product of the relative measurements in Tables V to VII obtained with electron microscopy multiplied by the corresponding values of the cell volumes. Although there was little difference between the normal myocytes in endocardial and epicardial regions, hypertension produced highly significant differences between these two populations of cells in nearly every structural characteristic.

The interstitial volume in myocardium, which ranged from 15.1 to 20.6 percent, was subdivided morphometrically into three components (Table IX). Significant differences were principally found in the volume percent of capillary lumen, which is nearly twofold greater in the epicardium than in the endocardium. However, the volume percent of endothelium is not proportionately larger, implying a thinner endothelial lining of the epicardial capillaries.

The volumes of interstitial components per myocyte were calculated from their volume percentages and the mean volumes of myocytes. On this cell basis epicardial myocytes were surrounded by 77 percent more interstitium than endocardial myocytes. Because the number of myocytes was unchanged in the hypertrophied left ventricle of hypertensive rats, the percent increases in the volume of interstitium indicate directly the amount of interstitial enlargement: 55 percent of the endocardium and 34 percent in the epicardium. When these values of interstitial growth are combined with the corresponding values of myocyte hypertrophy, 21 and 37 percent (Table VIII), the total myocardial hypertrophy is 26 percent in the endocardium and 37 percent in the epicardium.

Capillary luminal area and volume and length: The total luminal area and number of capillary profiles measured with low power electron micrography are listed in Table X. The quotient of these figures yields the mean area of capillary lumen per profile. These transverse capillary areas were significantly larger in the epicardium. Furthermore, the values in each region of the myocardium were increased in hypertension. The orientation of myocardial capillaries was almost entirely perpendicular to the transverse plane of the sections in which these data were collected, that is, parallel to the long axis of the myocytes. Consequently, the total volume of capillary lumen divided by the average area of luminal profile is a measure of the length of these channels. The length of capillaries per unit volume was uniform throughout the myocardium in both the control and hypertensive rats but was shorter in the hypertensive rats. In view of the homogeneous distribution of capillary length density, the total length of capillaries in the left ventricle may be determined in the same way that the number of myocytes was calculated earlier. On this basis the normal ventricle contains 3.10 ± 0.17 km of capillary whereas the hypertrophied ventricle contains 3.12 ± 0.17 km, indicating no significant change in length. Because no information is available about the average length of a capillary unit in the normal or hypertrophic rat heart, these data do not imply that the number of capillaries is also constant.

Additional numeric characteristics of the capillary distribution can also be derived from the available data. First, from the number of myocyte profiles counted (Table V), their number per square millimeter of myocardium can be compared with the corresponding

TABLE IX

Volume Composition of Interstitium in Left Ventricular Myocardium*

	Normotensive Rats	Hypertensive Rats	*P* Value
Volume percent of myocardium			
Interstitium exclusive of capillaries			
Endocardial†	8.7 ± 1.0	12.7 ± 1.5	<0.1
Epicardial	11.3 ± 2.4	10.8 ± 1.2	<0.9
P value	<0.4	<0.4	
Capillary lumen			
Endocardial	3.2 ± 0.6	3.4 ± 0.5	<0.9
Epicardial	6.1 ± 0.8	6.8 ± 0.9	<0.7
P value	<0.02	<0.01	
Endothelial cells			
Endocardial	3.2 ± 0.2	2.6 ± 0.2	<0.1
Epicardial	3.2 ± 0.1	2.6 ± 0.1	<0.05
P value	<1.0	<1.0	
Interstitial volumes/myocyte (μm^3)			
Interstitium			
Endocardial	1,840 ± 180	2,860 ± 230 (55)	<0.005
Epicardial	3,270 ± 490	4,380 ± 350 (34)	<0.1
P value	<0.02	<0.005	
Capillary lumen			
Endocardial	391 ± 75	523 ± 80 (34)	<0.3
Epicardial	970 ± 180	1,470 ± 220 (52)	<0.2
P value	<0.02	<0.001	
Endothelial cells			
Endocardial	391 ± 29	400 ± 35 (2)	<0.9
Epicardial	508 ± 66	564 ± 42 (11)	<0.6
P value	<0.2	<0.02	

* Data are mean values ± standard error.
† Endocardial and epicardial regions of left ventricular myocardium.
P = probability.

TABLE X

Capillary Distribution in Left Ventricular Myocardium

	Normotensive Rats	Hypertensive Rats	*P* Value
Area of capillary lumens (μm^2)			
Endocardial	2578	4768	
Epicardial	7715	9567	
no. of capillary profiles			
Endocardial	396	529	
Epicardial	624	542	
Luminal area/profile (μm^2)			
Endocardial	6.5 ± 1.2*	9.0 ± 1.5	<0.3
Epicardial	12.4 ± 1.4	17.7 ± 2.2	<0.1
P value	<0.01	<0.005	
Profiles/mm^2 =			
Length (mm)/mm^3			
Myocardium			
Endocardial	4850 ± 180	3730 ± 140	<0.001
Epicardial	4910 ± 360	3860 ± 360	<0.1
P value	<0.9	<0.8	
Interstitium			
Endocardial	32100 ± 2900	20000 ± 1700	<0.005
Epicardial	23900 ± 2500	19100 ± 1300	<0.1
P value	<0.1	<0.7	
no. of myocyte profiles/mm^2 myocardium			
Endocardial	5470 ± 270	4110 ± 110	<0.001
Epicardial	6520 ± 560	3910 ± 260	<0.001
P value	<0.2	<0.5	
no. of capillaries/no. of myocytes			
Endocardial	0.887 ± 0.005	0.908 ± 0.042	<0.8
Epicardial	0.753 ± 0.085	0.987 ± 0.113	<0.2
P value	<0.3	<0.6	
Intercapillary distance (hexagonal array) (μm)			
Endocardial	15.4	17.6	
Epicardial	15.3	17.3	

* Endocardial and epicardial regions of left ventricular myocardium.
P = probability
† Data are the mean values ± standard error.

frequency of capillary profiles. The ratio of capillary profiles to myocyte profiles, shown next in Table X, did not vary significantly, ranging from 0.75 to 0.99. Second, the average intercapillary distance can be estimated assuming some regular spatial distribution. A hexagonal lattice of capillary profiles is considered more appropriate than a square array. This preference in the distribution of myocardial capillaries is based on the surface to volume ratio of myocytes (Table V). In a hexagonal pattern the center to center distance between capillaries will be $1.075/\sqrt{N_{Acap}}$, where N_{Acap} is the number of capillary profiles per unit area. This distance between capillary profiles is, as expected, greater in the hypertensive animals as a result of the hypertrophy of myocytes and interstitium.

Measured relations between capillary luminal surface and other myocardial components are given in Table XI. No significant differences were found in the concentration of capillary luminal surface in the myocardium as a whole, in the interstitial compartment alone or in relation to the volume of contractile cells. Hypertensive hypertrophy appears to induce a proportional increase in capillary luminal surface area in both the endocardium and epicardium. The normally greater capillary surface area per myocyte in the epicardium becomes statistically significant in hypertension.

Discussion

Previous morphometric studies of cardiac hypertrophy[3–6] describe changes at the cell level only in terms of relative volume and surface area measurements. Our present study employed a method for determining mean cell volume that permitted the calculation of many structural parameters of myocytes and their organelles in absolute values of volume, surface area and number per cell. This procedure yields measurements of the mean cell volume per nucleus that are identical to those of the absolute mean volume per cell in mononucleate populations. There is conflicting evidence concerning the frequency of multinucleate myocytes in the myocardium of the rat. Histologic sections of rat heart, including those investigated in our study, reveal mostly mononuclear muscle cells.[18] However, cell suspensions from the dissociated ventricular wall show 80 percent or more binucleate muscle cells.[19–22] In several other species binucleate cardiac myocytes are usually absent at birth but accumulate in greater numbers during development.[23–26] Counts taken in our study revealed 2 to 4 percent binucleate profiles. However, the proportion of binucleate images seen in tissue sections is always less than the true frequency of binucleate cells because some fraction of these cells can appear mononucleate when the second nucleus is not included in the plane of sectioning. The magnitude of this fraction depends on

TABLE XI

Relations Between Capillary Luminal Surface and Myocardial Components*

	Normotensive Rats	Hypertensive Rats	*P* Value
Capillary luminal surface (mm^2)/ mm^3 myocardium			
Endocardial	63.4 ± 5.8	64.8 ± 5.7	<0.9
Epicardial	76.6 ± 7.6	78.5 ± 7.8	<0.9
P value	<0.3	<0.2	
mm^3 interstitium			
Endocardial	420 ± 28	348 ± 38	<0.2
Epicardial	372 ± 48	389 ± 40	<0.8
P value	<0.5	<0.5	
mm^3 myocytes			
Endocardial	74.6 ± 6.9	79.6 ± 7.1	<0.7
Epicardial	96.5 ± 9.8	98.2 ± 9.9	<0.9
P value	<0.1	<0.2	
myocyte × 10^6			
Endocardial	770 ± 77	996 ± 97	<0.2
Epicardial	1,220 ± 200	1,700 ± 210	<0.2
P value	<0.1	<0.01	

* Data are the mean values ± standard error.
P = probability.

the size, spacing and orientation of the paired nuclei and also on the thickness and orientation of the tissue slices.[27] Although the percentages determined in our study are based only on relatively small counts and are smaller than the experimental errors involved, the values of the measured cell volumes per nucleus have been multiplied by the appropriate factor for the presence of binucleate cells to obtain the best estimates of the mean cell volumes of ventricular myocytes. Although the difference between the apparent frequencies of binucleate myocytes in tissue sections and isolated cell preparations remains unexplained, the mean cell volume per nucleus recently measured from isolated cells[20] is nearly the same as that determined from sections in our study. Tissue sections must be used to obtain meaningful morphometric data concerning other constituents of myocardium, specifically the interstitium.

Endocardial versus epicardial hypertrophy in hypertension: The data indicate that normal ventricular myocardium has a greater concentration of contractile tissue in the endocardial layers than in the epicardial layers, possibly because of the greater wall tension in the inner layers of the ventricle according to the law of Laplace.[28] In hypertension the normally larger epicardial myocytes enlarge 37 percent whereas those in the endocardium enlarge 21 percent. However, the growth of interstitial elements in the endocardium (55 percent) is disproportionately greater than that in the epicardium (34 percent), resulting in a more nearly uniform distribution of the volume ratio between myocytes and interstitium. The 30 percent overall increase in left ventricular mass induced by hypertension is composed of 26 percent hypertrophy of the endocardial layers and 37 percent hypertrophy of the epicardial layers. This growth occurs with no evident changes in the number of myocytes, which is consistent with autoradiographic studies showing little or no DNA synthesis within hypertrophying myocytes.[2,29,30]

Characteristics of cell reaction in hypertrophy: The volume fractions of mitochondria and myofibrils, which together compose approximately 87 percent of myocyte cytoplasm, shift slightly in hypertrophy so that their volume ratio is decreased, particularly in endocardial cells. The volume ratio of mitochondria to myofibrils increases significantly in the early stages of hypertrophy.[6,31] This ratio decreases progressively with prolonged hypertrophy and may lead to a deficient energy supply that could compromise heart muscle contractility.

Combining conventional "per unit volume" morphometric measurements with measurements of mean cell volume enables the analysis of tissue heterogeneity and cell hypertrophy from the viewpoint of average cell characteristics and the amount of organelle growth per cell. This approach shows that the cell reaction in hypertrophy (summarized in Table VIII) is one in which myofibril, smooth endoplasmic reticulum and T system growth significantly exceeds the mean cell growth whereas nuclear, mitochondrial and matrix growth is relatively much less. The absolute increase in smooth endoplasmic reticulum volume and surface is nearly double the increase in myofibrillar mass, possibly compensating for the reduced calcium binding capacity of this system in hypertrophy.[32] In hypertension the volume of the T system was increased 62 percent in endocardial myocytes and 99 percent in those of the epicardium. Furthermore, the surface area of internalized basement membrane lining the external surface of the T system should be increased proportionately 61 and 81 percent, respectively, in endocardial and epicardial myocytes. Although the rat may be an exception,[33] the T system in cardiac cells has a significant role in calcium metabolism related principally to the calcium binding capacity of its basement membrane.[34]

The T system effectively increases the total external surface area of myocytes and may also be important in determining the speed of conduction of the action po-

tential across the myocardium.[35] In general, enlarged cells having less surface area to depolarize per unit volume conduct at a faster rate.[36] In contradistinction to the T system, the surface area of the external sarcolemma of cardiac myocytes was expanded relatively much less during hypertrophy because the cells assumed a generally broader configuration. However, the summation of T system and external sarcolemma was found to vary nearly in proportion to the differences in myocyte volume (Table VIII). A similar proportionality has also been observed in normal growth as well as in hypertrophy.[4,37] These observations suggest that overall increases in cell surface membrane including the T system, resulting in an increase in total membrane capacitance, may minimize electrophysiologic changes during growth and hypertrophy.

Myocardial capillaries in hypertensive hypertrophy: The number of capillary profiles per square millimeter in the normal myocardium is nearly identical in endocardial and epicardial areas and agrees well with previous estimations inferred from microcinematographic studies.[38–41] The mean cross-sectional area of capillaries in the epicardium is twice that in the endocardium with the consequence that the capillary volume (luminal) is double the regional myocardial volume. Capillary volume per myocyte is 2.5 times greater in the epicardium where the cell concentration is lower. The luminal surface area of capillary endothelium available for oxygen transport in control animals is 58 percent greater for the epicardial myocytes. As a result of hypertensive hypertrophy, the myocardial capillaries exhibit increases in volume, mean cross-sectional area and luminal surface in both the endocardium and epicardium but no change in the length of capillaries in either region. The latter observation is consistent with results showing no increase in capillary number in the ventricular myocardium after both short and prolonged periods of renal hypertension.[42] The absolute increases in capillary volume and surface were each somewhat greater in both endocardial and epicardial regions than the overall enlargement of the myocardium. These disproportionate increases could offset the greater path length required for molecular diffusion as a result of the observed 15 percent increase in mean intercapillary distance. Cardiac hypertrophy in the dog is associated with significant increases in myocardial transcapillary exchange rates that are presumably related to changes or enlargement of the capillary luminal surface.[43]

There appears to be little qualitative difference in the structural composition of normal endocardial versus epicardial myocardium. However, our study demonstrates that a unit volume of endocardium contains 27 percent less interstitial space and 30 percent more cells that are 18 percent smaller in their average size. The measured volume of capillary lumen in the endocardium is only 52 percent of that of an equivalent amount of tissue in the epicardium, the difference being related entirely to the smaller average cross-sectional area of these channels. In addition, capillary surface is 17 percent less in the endocardial region.

Endocardial and epicardial cell growth responses in hypertrophy: In the brief period of hypertension examined in our study the endocardial and epicardial layers of the ventricular wall have responded differently with generally a greater change in the epicardium. Compared with that in the epicardium, the overall tissue enlargement in the endocardium was 30 percent less, the expansion of its capillary lumen 39 percent less and the increase in its contractile component 49 percent less. Capillary surface in the endocardium was expanded by a 32 percent smaller increment. Myocytes of the endocardium responded with 43 percent less hypertrophy and with volume increases of myofibrils and mitochondria that were 30 and 75 percent less, respectively. Augmentation of the volumes and surface areas of the smooth endoplasmic reticulum and T system in endocardial myocytes ranged from 25 to 50 percent less than that found in epicardial cells. This difference implies that the endocardial myocytes are somehow limited and may not have achieved a compensatory growth fully proportional to the increased work load. Epicardial myocytes may have responded to a greater degree to provide the necessary total increment in ventricular function. The different response capacities of the endocardium and epicardium either may be an intrinsic property of the myocytes or could be related to differences in the structure and function of the microcirculation.

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Echocardiographic Dimensions in Borderline and Sustained Hypertension

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Echocardiographic dimensions and hemodynamic indexes were determined in 42 patients with borderline hypertension and in 22 with sustained hypertension and the results were compared with findings in 33 normal subjects. In patients with borderline hypertension the thickness of the interventricular septum (IVS) was significantly increased ($P < 0.001$), whereas the posterior wall (PW) thickness remained within normal range. The IVS/PW ratio was significantly elevated ($P < 0.001$) and was correlated negatively with the cardiac index ($P < 0.01$) and positively with the preejection period ($P < 0.01$). In patients with sustained hypertension a symmetric cardiac hypertrophy was observed, and there was a significant positive correlation between the IVS/PW ratio and diastolic pressure ($P < 0.05$). The study suggested that (1) in sustained hypertension the symmetric cardiac hypertrophy was secondary to a progressive increase in pressure load, whereas (2) in borderline hypertension the asymmetric cardiac hypertrophy could not be directly related to the level of blood pressure and was probably associated with abnormalities of the sympathetic nervous system.

Two types of cardiac hypertrophy have been described in spontaneously hypertensive rats[1–3]: (1) At an early stage of the disease, an increase in left ventricular weight is found before arterial pressure has reached hypertensive levels[2,3]; and (2) at a later stage of the disease, hypertension is more marked and cardiac hypertrophy appears to be more readily related to the level of blood pressure and, therefore, mainly as a response to the progressive increase in pressure load. In human hypertension, the latter pattern has been extensively studied.[4,5] In contrast, there have been few systematic studies of cardiac hypertrophy in early hypertension, particularly in borderline hypertension.

Recently, noninvasive techniques enabled cardiac performance to be more readily evaluated in man.[6,7] In addition, echocardiography provided a reliable method for measuring ventricular wall thickness.[6] In the present study, we evaluated echocardiographic dimensions and systolic time intervals in patients with borderline and sustained hypertension in comparison with normal subjects.

Methods

Patients: The study group included 64 men with either borderline or sustained hypertension and 33 normotensive men in whom extensive clinical and laboratory investigations revealed no evidence of cardiovascular disease. The diagnosis of borderline hypertension was based on the finding during a 12 month follow-up period of at least one diastolic pressure value equal to or greater than 90 mm Hg and of at least another diastolic reading greater than 90 mm Hg. Sustained hypertension was defined as a diastolic pressure consistently greater than 100 mm Hg in the absence of therapy. All diagnoses were based on outpatient blood pressure recordings. All subjects were either untreated or had discontinued therapy at least 1 month before the study.

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All subjects were hospitalized for 6 days and placed on a diet of 110 mEq/day of sodium. Investigations included determination of blood and urinary electrolyte levels, catecholamines, endogenous creatinine clearance and timed intravenous urography. All hypertensive patients were diagnosed as having essential hypertension and had no evidence of renal, neurologic or cardiologic involvement; all had regular sinus rhythm without evidence of left or right bundle branch block (Table I). The protocol was approved by INSERM (Institut National de la Santé et de la Recherche Médicale). All subjects freely consented to the investigation after a detailed description of the procedures was given.

Hemodynamic procedures: On the 3rd day of the patient's hospitalization, hemodynamic studies were performed after an overnight fast and with the patient in a supine position. No premedication was administered. With the patient under local procaine anesthesia, a polyethylene catheter was introduced through an antecubital vein, and an 18 gauge, thin-walled needle was inserted into a brachial artery. Cardiac output was determined in duplicate with the dye-dilution method and expressed in reference to body surface area; the procedures utilized were previously described in detail.[8] The pressure transducers and recording system (Thomson-Telco apparatus) were calibrated before each exploration; the 0 reference level was mid sternal.

Systolic time intervals[9]: Systolic time intervals were measured from simultaneous recordings (at a paper speed of 100 mm/sec) of the electrocardiogram (lead II), phonocardiogram and carotid arterial pulse tracing.[9] For phonocardiography, the microphone was placed over the upper part of the precordium in the optimal position for recording the initial high frequency vibrations of the second heart sound. The carotid arterial tracing was obtained with a Telco-pulse sensor placed over the maximal pulsation of the right external carotid artery. All recordings were obtained with the patient in the supine position after a 15-minute rest period, before the hemodynamic study. Total electromechanical systole ($Q\text{-}S_2$) and left ventricular ejection time were measured to the nearest 5 msec from at least 10 consecutive cycles.[7,9] The preejection period was obtained by subtracting the left ventricular ejection time from $Q\text{-}S_2$; because the preejection period does not vary to any significant extent with heart rate, no correction factor was needed.[10] Care was taken to ensure that the beginning and end of recordings always coincided with the same phase of respiration. No patient had a bifid pulse in the external carotid pulse recording.

Echocardiography: This study was performed with a Picker echograph, using a 2.25 megahertz unfocused transducer; photographs of the echographic display were taken directly from the face of the oscilloscope. Patients were examined in the supine or partial left lateral position. The transducer was placed in the fourth or fifth intercostal space lateral to the left sternal border. When the characteristic rapid motion of the anterior leaflet of the mitral valve had been identified, the transducer was directed inferolaterally toward the apex of the ventricle until the appropriate location[6] was found. In this plane, there were faint echoes from the anterior wall of the right ventricle, a band of echoes from the interventricular septum and another band of echoes from the posterior wall of the left ventricle. Appropriate adjustments of the damp, reject and gain modalities were made to obtain a good definition of the walls and left ventricular cavity. Patients in whom adequate echocardiograms could not be obtained (eight cases) were excluded prior to any determinations; all readings were performed by two observers who did not know the subject's status.

Posterior wall thickness and septal wall thickness were measured in end-diastole before atrial contribution to ventricular filling. The end-diastolic diameter was measured as a vertical line drawn through the peak of the QRS complex. The end-systolic diameter was defined as the smallest distance separating the interventricular septum and left ventricular posterior wall. Signals that appeared only during systole or diastole and that were not present continuously throughout an entire cardiac cycle were rejected as not representative of true septal thickness.

To minimize the effects of respiration, echocardiographic measurements were averaged from ten consecutive cardiac cycles. The echocardiograms were analyzed independently by two observers who did not know the subjects' condition and blood pressure level. In all cases, the measurements agreed within 5 percent. None of the 57 patients studied had abnormal systolic anterior movement of the anterior mitral cusp, even after administration of amyl nitrite.

Plasma renin activity: Plasma renin activity was determined in only 18 patients, 9 with borderline and nine with sustained hypertension. Blood samples were taken during the hemodynamic study with the patient in the supine position; sodium intake was 110 mEq/day. Renin activity was determined by autoincubation of plasma followed by radioimmunoassay of angiotensin I, as previously described.[11]

Results

Hemodynamic indexes and systolic time intervals (Table II): In subjects with borderline hypertension, both blood pressure ($P < 0.001$) and cardiac index (P

TABLE I

Clinical Characteristics*

	Normal Subjects	Patients With Borderline Hypertension	Patients With Sustained Hypertension
Patients (no.)	33	42	22
Age (yr)	29.3 ± 1.2	27.3 ± 1.2	32.7 ± 4.1
Weight (kg)	65.2 ± 1.8	72.3 ± 1.2†	73.2 ± 5.9†
Body surface area (m^2)	1.76 ± 0.03	1.84 ± 0.02†	1.85 ± 0.06†

* Values are ±1 standard error of the mean.
† P (probability) <0.01 in comparison with normal subjects.

TABLE II

Hemodynamic Measurements and Systolic Time Intervals*

	Normal Subjects	Patients With Borderline Hypertension	Patients With Sustained Hypertension
Patients (no.)	33	42	22
SAP (mm Hg)	125.9 ± 2.4	154.3 ± 4.0†	184.8 ± 5.7†
DAP (mm Hg)	70.3 ± 1.7	77.8 ± 1.8†	105.1 ± 3.9†
CI (ml/min/m^2)	3434 ± 8.2	3771 ± 112‡	3453 ± 205
HR (beats/min)	70.5 ± 1.6	74.3 ± 1.8	72.1 ± 1.9
PEP (msec)	104.4 ± 5.7	90.6 ± 2.7†	116.5 ± 2.5‡
LVET (msec)	285.3 ± 3.9	273.6 ± 3.5‡	274.1 ± 8

* Values are ±1 standard error of the mean. Since heart rates were similar in the three groups of patients, systolic time intervals were not corrected for heart rate.[10]
† P (probability) <0.001 in comparison with normal subjects.
‡ P <0.05 in comparison with normal subjects.
CI = cardiac index; DAP = diastolic arterial pressure; HR = heart rate; LVET = left ventricular ejection time; PEP = preejection period; SAP = systolic arterial pressure.

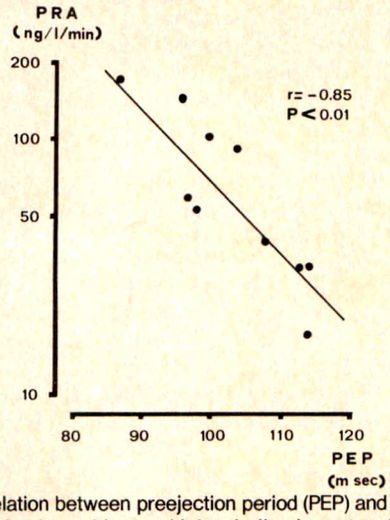

FIGURE 1. Relation between preejection period (PEP) and plasma renin activity (PRA) in nine subjects with borderline hypertension (semilogarithmic scale). *P* = probability; r = correlation coefficient.

<0.05) were significantly increased. Heart rate was within normal range. Preejection period was significantly reduced ($P < 0.001$) and was negatively correlated with plasma renin activity ($r = -0.85$) (Fig. 1). Left ventricular ejection time was slightly reduced ($P < 0.05$). Results in patients with sustained hypertension showed a different pattern. Cardiac index and heart rate were within normal limits, whereas the preejection period was prolonged ($P < 0.05$) and showed no significant correlation with plasma renin activity ($r = 0.13$). Left ventricular ejection time was within normal range.

Echocardiographic dimensions (Fig. 2; Tables III and IV): In normal subjects, a positive correlation was observed between interventricular septal (IVS) and posterior wall (PW) thickness ($r = 0.60$), so that the IVS/PW ratio remained within a range of 0.89 to 1.10 (mean ± standard error of the mean 0.96 ± 0.02). Figure 2 indicates the 90 percent confidence limits of the normal relation between the thickness of the two walls. Judged against this background, the interventricular septal thickness in subjects with borderline hypertension was significantly increased ($P < 0.001$), whereas the posterior wall thickness remained within normal range (Table III). The IVS/PW ratio was therefore significantly increased ($P < 0.001$); it remained within the confidence limits of the normal relation in only 6 patients, but exceeded them in the other 18 (Fig. 2). The IVS/PW ratio was significantly correlated (1) inversely with cardiac index ($r = -0.59$; $P < 0.01$) and (2) positively with preejection period ($r = 0.51$; $P < 0.01$); it did not correlate with either diastolic pressure ($r = 0.24$) or plasma renin activity ($r = -0.35$) (Table IV).

In patients with sustained hypertension, interventricular septal and posterior wall thicknesses were significantly increased ($P < 0.001$ and $P < 0.01$, respectively) (Table III). Their ratio (IVS/PW) remained

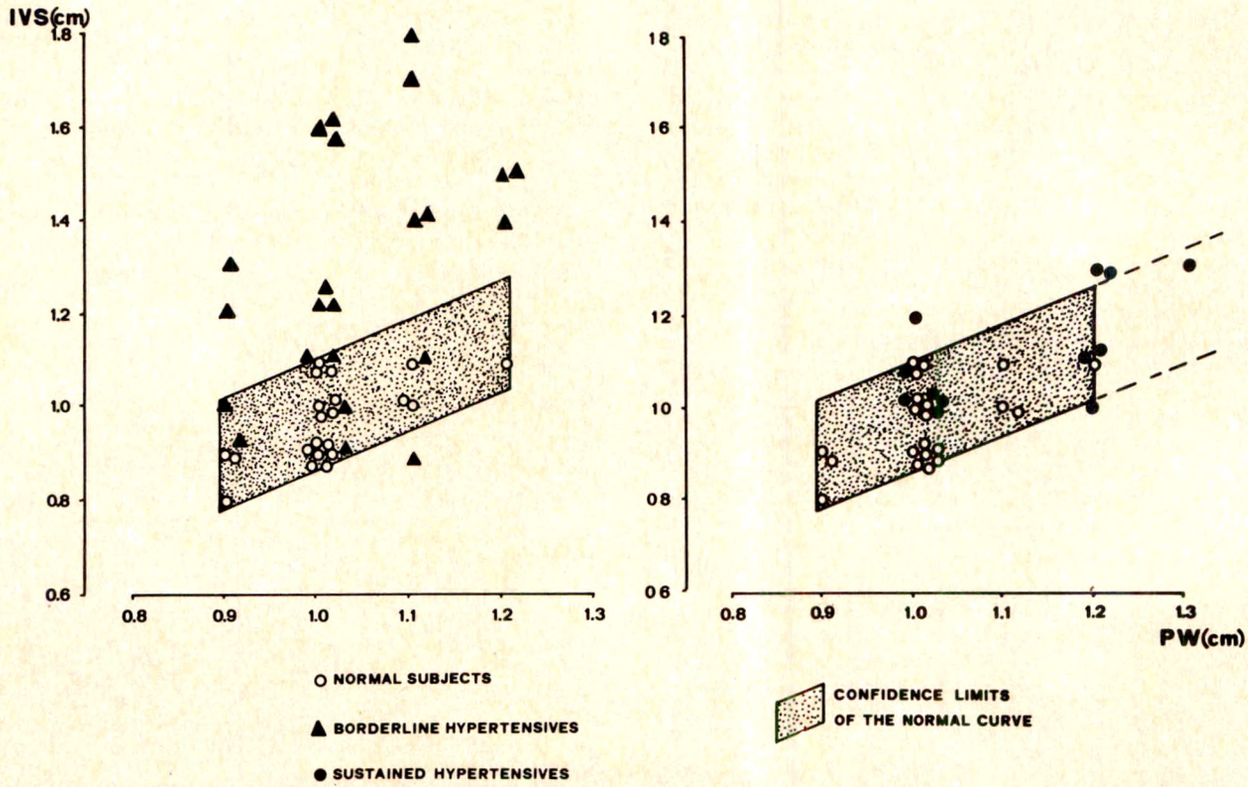

FIGURE 2. Relation between posterior wall thickness (PW) and interventricular wall thickness (IVS) in normal subjects, patients with borderline hypertension and those with sustained hypertension. A significant positive relation was observed in normal subjects ($r = 0.60$) and in patients with sustained hypertension ($r = 0.60$) but not in those with borderline hypertension. When the groups of normal subjects and the patients with sustained hypertension were combined, the correlation coefficient reached 0.75.

within or along linear prolongation of confidence limits of the relation of intraventricular septal to posterior wall thickness as defined in normal subjects (Fig. 2). The ratio showed no significant correlation with cardiac index, preejection period or plasma renin activity, but there was a significant positive correlation with diastolic pressure ($r = 0.62$; $P < 0.05$) (Fig. 3).

End-systolic (ES) and end-diastolic (ED) diameters were not different from normal diameters in either subjects with borderline hypertension or in patients with sustained hypertension, except for the end-systolic diameter, which was significantly increased in patients with sustained hypertension (Table III). The relative reduction in diameter [(ED − ES/ED)] was equal in normotensive subjects and in patients with borderline hypertension (0.33 ± 0.08 versus 0.30 ± 0.06); it showed some decrease in patients with sustained hypertension (0.26 ± 0.09), but the difference was not statistically significant.

Discussion

Asymmetric septal hypertrophy in borderline hypertension: Echocardiography has introduced a new dimension in the study of hypertensive heart disease.[5,6,12,13] Techniques have been well standardized and values for normal subjects in this series are in agreement with those of others.[5,6,12] The unexpected finding in our study was the preponderance of asymmetric septal hypertrophy and increased interventricular septal/posterior wall ratio (IVS/PW) among patients with borderline hypertension. This raises many important questions. An association between asymmetric septal hypertrophy and hypertension has previously been reported in patients with muscular subaortic stenosis.[14,15] The latter diagnosis seemed unlikely in our patients because of the negative response to amyl nitrite. Recent echocardiographic studies in hypertension indicated a 10 to 30 percent incidence rate of asymmetric septal hypertrophy in two different groups of patients with sustained hypertension.[5,16] Our findings

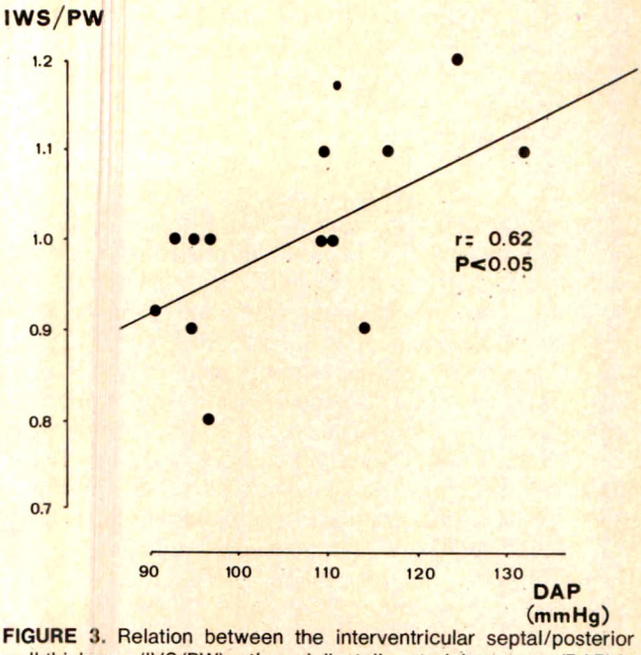

FIGURE 3. Relation between the interventricular septal/posterior wall thickness (IVS/PW) ratio and diastolic arterial pressure (DAP) in patients with sustained hypertension.

strongly suggest that asymmetric hypertrophy of the left ventricle was more characteristic of borderline hypertension in young patients than of sustained hypertension with more accentuated pressure elevation.

To the extent that the left ventricular response to increased pressure load is usually expected to be a uniform or symmetric hypertrophy, the asymmetric septal thickness in borderline hypertension was somewhat unexpected. It is conceivable that the increased septal thickness represents the initial stages of hypertrophy; the difference in radius of curvature between the septal and lateral walls of the left ventricle would lead to greater tension in the septal wall.[17] However, explanations based on pressure load do not appear to

TABLE III

Echocardiographic Dimensions*

	Normal Subjects	Patients With Borderline Hypertension	Patients With Sustained Hypertension
Patients (no.)	21	24	12
Interventricular septal (IVS) thickness (cm)	0.97 ± 0.02	1.29 ± 0.05†	1.12 ± 0.04†
Posterior wall, (PW) thickness (cm)	1.01 ± 0.01	1.04 ± 0.02	1.11 ± 0.03‡
IVS/PW ratio	0.96 ± 0.02	1.25 ± 0.09†	1.01 ± 0.03
End-diastolic dimension (cm)	4.49 ± 0.10	4.52 ± 0.09	4.63 ± 0.10
End-systolic dimension (cm)	3.14 ± 0.09	3.15 ± 0.07	3.47 ± 0.11§

* Values are ±1 standard error of the mean.
† P (probability) <0.001 in comparison with normal subjects.
‡ P <0.01 in comparison with normal subjects.
§ P <0.05 in comparison with normal subjects.

TABLE IV

Correlation Coefficients of the Relations Between the IVS/PW Ratio and Hemodynamic Measurements in Patients With Borderline or Sustained Hypertension

	Correlation Coefficient (r)	
Variable Studied	Patients With Borderline Hypertension (no. = 24)	Patients With Sustained Hypertension (no. = 12)
CI (ml/min per m^2	−0.59*	−0.09
PEP (msec)	+0.51*	+0.01
DAP (mm Hg)	+0.24	+0.62†

* P <0.01.
† P <0.05.
‡ Observations were available only in 18 patients, 9 with borderline hypertension and 9 with sustained hypertension.
CI = cardiac index; DAP = diastolic arterial pressure; PEP = preejection period.

fit with the absence of correlation in these patients between the IVS/PW ratio and diastolic pressure.

Factors influencing cardiac hypertrophy in borderline hypertension: Many factors other than arterial pressure could influence cardiac hypertrophy in hypertensive disease.[18] Studies in experimental animals have suggested possible links between cardiac hypertrophy and the sympathetic and the renin-angiotensin systems.[19,20] These relations were therefore looked for among our patients. Because no significant correlation was found between plasma renin activity and the IVS/PW ratio, it would be difficult to ascribe a major role to the renin system in asymmetric hypertrophy. In contrast, some of our results could point to some role of the adrenergic system in that context. Increased sympathetic activity has been reported a main characteristic of patients with borderline hypertension.[21–23] Our patients with asymmetric hypertrophy indeed had significantly increased cardiac output and reduced preejection period (Table II), which suggests increased cardioadrenergic drive.[7,10] Thus, in our patients with borderline hypertension, asymmetric hypertrophy (increased IVS/PW ratio) and signs of enhanced sympathetic activity were closely associated. However, association does not necessarily imply a causal relation; further, the association must be interpreted cautiously in view of the correlations observed between the IVS/PW ratio and hemodynamic indexes within the group of subjects with borderline hypertension. Among these, the positive correlation between the preejection period and IVS/PW ratio implies that other factors must also be important in determining the degree of septal hypertrophy.

Sustained versus borderline hypertension: Quite different from these findings were the pattern and the correlates of cardiac hypertrophy observed in patients with sustained hypertension. Our results are in agreement with those of previous echocardiographic studies[5,12,16]; patients with sustained hypertension comparable with ours had a moderate symmetric left ventricular hypertrophy.[5,12,16] Further, a significant correlation was observed between blood pressure and the IVS/PW ratio: the higher the pressure, the more the ratio tended toward unity, that is, the higher the degree of symmetry of hypertrophy (Fig. 3). These results strongly suggest that this echocardiographic pattern represents a progressive adaptation of the left ventricle to chronic pressure overload in patients with sustained hypertension.

Many hemodynamic differences between borderline and sustained hypertension have been reported by us,[8,24,25] and by other investigators.[21,23,26] These include differences in cardiac output, plasma volume and cardiovascular control mechanisms (for review see References 21, 25, and 26). Another difference, namely, the type of cardiac hypertrophy, became apparent in the course of this study. Folkow[27] has demonstrated the important dynamic role played by structural changes in resistance vessels in the evolution of hypertension. More recently the importance of structural cardiac changes was pointed out.[28,29] The contrast uncovered in this study, between asymmetric hypertrophy in borderline hypertension and the more uniform ventricular hypertrophy seen with higher diastolic pressure in sustained hypertension, might represent another important factor in the hemodynamic evolution of the disease. The causes and effects of these structural changes are not yet completely clear. The prevalence of asymmetric hypertrophy in the subjects with borderline hypertension who also have signs of increased adrenergic activity might suggest some role for the autonomic system in the increased interventricular septal/posterior wall thickness ratio.

Acknowledgment

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Left Ventricular Mass and Wall Thickness in Hypertension

Comparison of M Mode and Two Dimensional Echocardiography in Two Experimental Models

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The performance of noninvasive echocardiography, both M mode and two dimensional, was achieved in conscious dogs, allowing the study of direct anatomic-echocardiographic correlations of ventricular wall thickness and mass. Forty-three dogs, 33 with normotension and 10 with experimental hypertension, were studied. Good correlation between measurements of wall thickness was found between M mode echocardiography and corresponding anatomic sites in the interventricular septum ($r = 0.62$, $P < 0.01$) and in the posterior left ventricular wall ($r = 0.75$, $P < 0.01$); echocardiography consistently underestimated septal thickness by 1.9 mm ± 0.3 (standard error of the difference), and posterior wall thickness by 1.6 mm ± 0.2. In contrast, calculations of left ventricular mass from M mode tracings (D^3 formula) grossly overestimated left ventricular weight (+65 percent, $P < 0.001$).

Accuracy of calculated mass was significantly improved by two dimensional echocardiography. In 19 dogs, calculations based on both short and long left ventricular axes together with average wall thickness obtained from the septal, posterior and anterolateral walls led to a highly significant correlation with left ventricular weight ($r = 0.90$, $P < 0.0001$). Two dimensional echocardiography was particularly useful in defining the presence of left ventricular hypertrophy in dogs with experimental hypertension in which there was increased thickness of the anterolateral wall with little change in the septal and posterior walls.

Relatively little is known about the patterns of left ventricular hypertrophy in response to hypertension. Its rate of development, symmetry and type can vary widely among individual patients and different types of hypertensive disease.[1–4] Progress in these areas has been hampered by the lack of an experimental model for critically evaluating these structural changes in different types of hypertension. Echocardiography appeared useful in this respect. Information from M mode tracings correlated fairly well with hemodynamic angiographic measurements.[5–7] However, many of these calculations, angiographic as well as echocardiographic, were based on a series of assumptions, most notably the prolate ellipsoid hypothesis.[8] In addition, the M mode technique imposed the approximation, among others, that the left ventricular long axis was twice as large as any of the short axes[9] and the assumption that left ventricular wall thickness was uniform throughout the chamber. Moreover, very few studies have correlated direct anatomic determinations with echocardiographic measurements of wall thickness and mass; in man, these studies have necessarily been limited to terminally ill patients[10] or patients undergoing open heart surgery.[11] Trials in experimental animals have involved, for the most part, direct cardiac application of transducers in anesthetized open chest dogs.[12] Only the study of Mashino et al.[13] used surface echocardiography in the dog; calculations of stroke volume were correlated with indicator-dilution measurements, but the accuracy of left ventricular mass determinations was not assessed in relation to postmortem findings.

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Therefore, this study was undertaken, first, to define the reliability of echocardiographic determinations of left ventricular wall thickness and mass by making comparisons with direct measurements in dogs killed immediately after the noninvasive procedure. Furthermore, the accuracy of M mode echocardiography was determined by comparing the results with those obtained with two dimensional echocardiography. Introduction of the latter technique represented a significant advance in that it allowed unwarranted assumptions about ventricular diameter and wall thickness to be replaced by their actual determinations. The value of these assumptions could be tested in different conditions. The study was therefore not limited to normotensive dogs because left ventricular hypertrophy can alter geometry and invalidate conclusions based on the normal heart alone. Two experimental models of hypertension (deoxycorticosterone [DOC] injection and renal arterial stenosis) were also investigated in the same manner as the normotensive animals.

The results confirmed the need to evaluate echocardiographic measurements in different models of disease. The cube formula[14] was accurate in many normotensive dogs, but it fell far from the mark in dogs with experimental hypertension and irregular thickening of left ventricular walls.

Methods

Experimental animals: A total of 43 dogs were studied, 33 with normal blood pressure and 10 with hypertension induced by deoxycorticosterone injections[15] or renal arterial narrowing.[16] All dogs had noninvasive M mode echocardiographic records; in addition, 10 normotensive and 9 hypertensive dogs also had two dimensional echocardiograms. Blood pressure in the hypertensive animals was recorded by direct measurements through a chronically inserted right iliac catheter.[17]

Deoxycorticosterone hypertension was induced in four dogs by intramuscular injection of 25 mg Percorten® pivalate every 3 weeks. Excessive hypokalemia was avoided by maintaining the animals on a normal salt diet. Mean arterial pressure increased over 3 weeks from an average of 88 to 120 mm Hg; the dogs were followed up an average of 13 weeks (range 8 to 24). *Renovascular hypertension* in five dogs was induced using externally adjustable renal clamps.[16,18] Blood pressure increased more rapidly than with deoxycorticosterone and attained higher levels, averaging 150 mm Hg (range 120 to 180). The animals were killed after 4 weeks of sustained hypertension.

Echocardiography: M mode echocardiograms were obtained with a Picker 80–C ultrasonoscope and a 6 mm diameter, 3.5 megahertz nonfocused transducer. The two dimensional studies were performed with a Toshiba SSH–10A phased-array ultrasonic sector scanner; they were recorded, reviewed and analyzed on a 0.5 inch (1.27 cm) cassette video tape system. All echocardiographic studies were performed in conscious animals trained to lie still; excellent tracings can also be obtained, if needed, under light anesthesia with morphine and thiopenthal sodium. The tracings were obtained with the dog on its left side with the upper limbs extended; the transducer was placed over a shaved area at the second or third intercostal space at the *right* sternal border. An echocardiographic scan from the aorta to the left ventricle could be obtained by angulating the transducer from a superior and leftward position to an inferior and rightward position. This scan results in a picture resembling that obtained from the left sternal border in man and gives excellent delineation of the interventricular septum, posterior left ventricular wall, mitral valve, aorta, aortic valve and left atrium (Fig. 1).

A similar technique was used for the two dimensional echocardiograms. With the transducer placed in the second or third intercostal space at the right sternal border, the sector scan image plane was first oriented to the long axis of the left ventricle. The transducer was then rotated 90° clockwise to obtain a short axis view of the left ventricle. A short axis sweep was then performed by slowly angling the image plane from the aorta to the apex (Fig. 2).

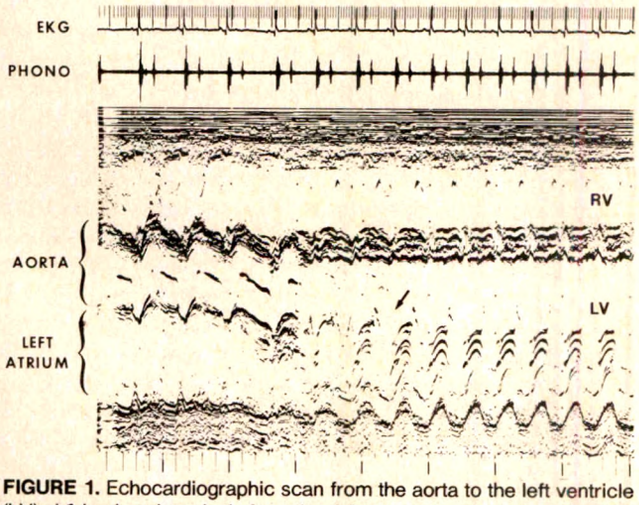

FIGURE 1. Echocardiographic scan from the aorta to the left ventricle (LV) obtained noninvasively from the right sternal border in the dog. EKG = electrocardiogram; phono = phonocardiogram; RV = right ventricle. **Arrow** points to anterior mitral leaflet.

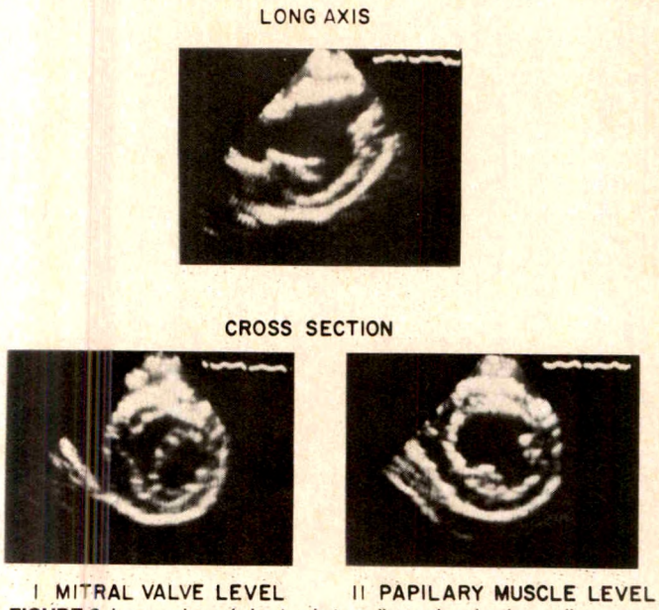

FIGURE 2. Long axis and short axis two dimensional echocardiograms obtained noninvasively from the right sternal border in the dog. **Upper figure,** measurements of the long axis were obtained. **Lower figures,** the anterioposterior and transverse diameters were measured as was the wall thickness.

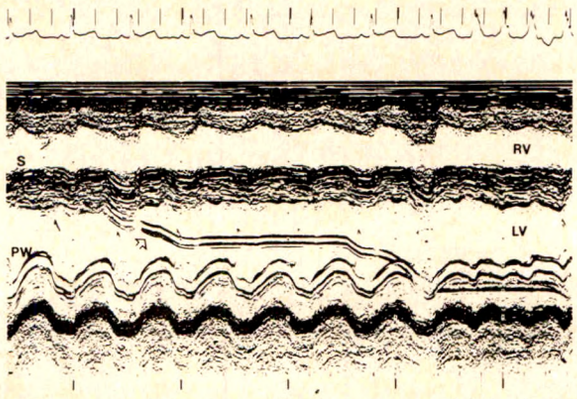

FIGURE 3. Left ventricular echocardiogram showing the tip of a needle (**open arrow**) penetrating the septum (S), the left ventricular cavity (LV) into the posterior wall (PW) of the left ventricle. RV = right ventricle. A chorda tendinea is seen parallel and proximal to the endocardial surface of the posterior wall.

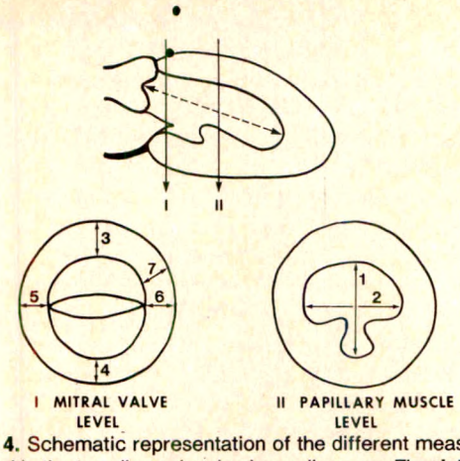

FIGURE 4. Schematic representation of the different measurements performed in the two dimensional echocardiograms. The **dotted arrow** represents the long axis of the left ventricle. **Arrows 1 and 2** correspond to the minor axes; **arrow 3** = septum; **arrow 4** = posterior wall; **arrow 5** = posterior septum; **arrow 6** = lateral wall; **arrow 7** = anterior wall.

Anatomic studies: Two separate studies were performed, one to evaluate the accuracy of echocardiographic determinations of wall thickness and the second to correlate calculated "left ventricular mass" with actual left ventricular weight. The first study involved 24 dogs, 23 with normotension and 1 with renal hypertension. After the initial tracing, the animals were anesthetized and a second M mode echocardiogram was obtained. The exact site of origin of the echocardiographic images in the interventricular septum and posterior left ventricular wall was marked with 0.1 cc of methyl blue injected through a pericardiocentesis needle (No. 18) introduced parallel to the transducer (Fig. 3). Wall thickness was measured at the level of these methyl blue markers.

The second study involved all 43 dogs; all were killed after receiving thiopenthal sodium anesthesia, with a saturated potassium chloride solution (15 ml intravenously). The hearts were immediately removed and washed thoroughly; both atria and the right ventricle were dissected away and the great vessels cut at the level of the semilunar valves. The left ventricle was dried with blotting paper and weighed on a precision balance.[19] In dogs that had two dimensional echocardiograms, two cross-sectional cuts of the left ventricle were obtained, one at the tip of the mitral valve and the other through the mid papillary muscle level; wall thickness was measured in five locations at these levels (Fig. 4).

Data analysis: *A. Echocardiographic measurements:* The two dimensional and M mode echocardiograms were interpreted without knowledge of the anatomic studies. All M mode measurements were taken according to the recommendations of the American Society of Echocardiography.[20] The specific variables examined by M mode echocardiography included thickness of the septum and posterior left ventricular wall as well as the end-diastolic and end-systolic diameter.

The specific variables examined in the two dimensional echocardiograms included the long axis of the left ventricle as well as its short anteroposterior and short lateral axes plus the wall thickness of the interventricular septum and the posterior, lateral and anterior walls (Fig. 4). These measurements were obtained at the level of both the mitral valve and the mid papillary muscle.

B. Calculations of left ventricular mass: Left ventricular mass was calculated in different ways. For M mode tracings, the D^3 method[14] was used with and without the correction factor of Teichholz et al.[21] Calculation of left ventricular mass from the two dimensional echocardiograms was based on different variants of the following formula[14]:

$$LVM = \left[\frac{(L + 2WT)\,(D_1 + 2WT)\,(D_2 + 2WT)}{2} - \frac{LD_1\,D_2}{2}\right] \times 1.05$$

where LVM is the left ventricular mass, L the end-diastolic long axis, D_1 the anteroposterior minor axis, D_2 the short transverse diameter, WT the wall thickness and 1.05 is the specific gravity of ventricular muscle. A first approach (LD^2) used the LD_1^2 and thickness of the posterior left ventricular wall only. The second variant ($LD_1\,D_2$) used the long axis, both short diameters, but again only the posterior wall thickness. The third formula ($LD_1D_2\,\overline{WT}$) used all three axes as well as the average of the wall thickness measured in five places at the level of the mitral valve (Fig. 4). The various calculations were tried to evaluate the relative importance of the many assumptions involved in the simple cube formula.[14]

Results

Correlation between M mode echocardiography and anatomic findings: *(1) Thickness of septal and posterior walls:* In 24 dogs direct anatomic-echocardiographic correlations of wall thickness were obtained by the methyl blue marker technique (Table I). The echocardiographic value for wall thickness was about 15 percent smaller than the anatomic measurement possibly because of changes in wall dimensions with death. However, there was a significant correlation between anatomic and echocardiographic wall thickness ($r = 0.62$ for the left ventricular septum and 0.75 for the posterior wall, $P < 0.01$ for both).

(2) Correlation of calculated mass with left ventricular weight: In these 24 dogs, the calculated mass (based on D^3) grossly overestimated the left ventricular weight (Table I); the same result was obtained in the entire group of 43 dogs. In the latter, left ventricular weight averaged 103.5 ± 26 g (standard deviation) versus a calculated mass of 170.7 ± 62 ($P < 0.001$). The correlation between the two ($r = 0.648$) was significant ($P < 0.01$) but the index of determination was low (42 percent). The Teichholz correction[21] reduced the dif-

TABLE I

M Mode Echocardiography: Correlation With Anatomic Findings in 24 Dogs

Index	M Mode	Autopsy	Δ %	*P*
Septal thickness (mm)	10.3 ± 1.5	12.3 ± 1.7	−16	<0.01
Posterior wall thickness (mm)	10.3 ± 1.6	11.9 ± 1.5	−13	<0.01
Left ventricular mass (g)	162 ± 58*	95 ± 24	+71	<0.001

* Based on "cube" formula.[14]

Values are average ± standard deviation; Δ% represents deviation of echocardiographic measurements from anatomic determinations; *P* = probability.

ference between calculated mass and weight to 23 percent but did not improve the correlation coefficient ($r = 0.646$, $r^2 = 42$ percent).

Two dimensional echocardiography: Two dimensional tracings were obtained in 19 dogs, 10 normotensive animals, 4 with deoxycorticosterone-induced hypertension and 5 with renovascular hypertension. Correlations with anatomic findings revealed an increasingly higher significance level, and the slope of the regression line approached the line of identity as assumptions implied in the D^3 formula were replaced by actual determinations of the long axis and the left ventricular wall thickness in different areas (Table II) (Fig. 5).

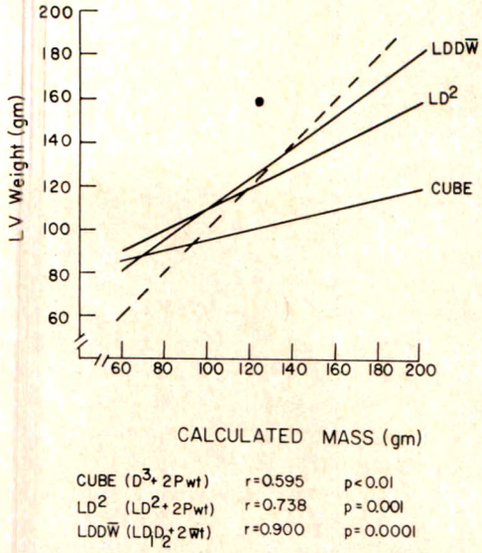

FIGURE 5. Relative accuracy of calculating left ventricular (LV) mass from M mode and two dimensional echocardiograms. There is a significant improvement of the correlation coefficient and a closer approximation to the line of identity (**dotted line**) as the cube formula is substituted by formulas that include long axis measurements (L), both minor axes (D_1 D_2) and the average wall thickness ($\bar{W}$). p = probability; r = correlation coefficient.

Discussion

This study demonstrates that excellent quality noninvasive M mode as well as two dimensional echocardiograms can be obtained in conscious dogs. Our results support the value of M mode echocardiography in determining wall thickness of the left ventricle but underline the serious limitations of this technique in calculating left ventricular mass. In contrast, an excellent approximation of left ventricular weight can be obtained with two dimensional echocardiography (Table II) (Fig. 5).

Limitations of M mode echocardiography: The good correlation between anatomic and echocardiographic wall thickness found in this study agrees with the data of others.[10,11] The consistent underestimation of wall thickness by echocardiography is possibly related to postmortem alterations as the left ventricle is emptied. In all dogs in which the posterior left ventricular wall was marked with methyl blue in vivo, the needle followed the same path through the right ventricle, the mid portion of the interventricular septum and the posterobasal wall between the papillary muscles. Thus, measurements of the short anteroposterior ventricular diameter and wall thickness were obtained in a reproducible way in limited areas with this technique.

However, calculation of left ventricular mass from M mode tracings was not precise, which is not surprising in view of the limited information these tracings afforded regarding complex three dimensional ventricular geometry. Besides, in evaluating hypertrophied hearts, M mode echocardiography is limited not only because of its restriction to a single ventricular diameter but also because measurement of the thickness of the septal and posterior walls, which are the only areas that can be visualized with this method, may not demonstrate changes occurring in other areas. Left ventricular hypertrophy in hypertension was not necessarily con-

TABLE II

Correlation Matrix of Left Ventricular Weight With Calculation of Left Ventricular Mass by Various Formulas

Statistical Index	M Mode Tracings		Two Dimensional Tracings		
	D_3	Teichholz[21]	LD_1^2	LD_1D_2	$LD_1D_2\bar{WT}$
Correlation coefficient (*r*)	0.595	0.573	0.736	0.775	0.900
Probability (*P*) value	<0.01	=0.01	=0.001	=0.001	<0.0001
Determination index (%)	35.4	32.8	54.2	60.0	81
Standard deviation of regression	54.3	28.4	26.0	23.0	14.1

Left ventricular mass calculations are based on Troy's formula.[14] For $LD_1D_2\bar{WT}$, the mean wall thickness ($\bar{WT}$) was the average from five different sites (Fig. 4). In all the others, the only thickness used was that of the posterior wall. The transverse short axis (D_2) was used in the last two formulas. The actual long axis (L) of the left ventricle was used in all the two dimensional calculations. For the M mode calculations, the long axis was assumed to be twice as large as the anteroposterior diameter (D).

centric or symmetric.[22] Hence, although M mode echocardiography accurately measures the limited areas that it can visualize, it is of limited value in the overall evaluation of the left ventricle. The greater the number of assumptions implicit in a formula meant for calculating left ventricular mass, the greater the possibility of error; this applied particularly to diseased hearts in which hypertrophy may be asymmetric.

Accuracy of two dimensional echocardiography in the diagnosis of left ventricular hypertrophy: In contrast with M mode tracings, an excellent approximation of left ventricular weight was obtained with two dimensional echocardiography not only in normotensive but also in hypertensive dogs. In addition to determination of the minor anteroposterior diameter and both septal and posterior wall thicknesses, this technique allows the left ventricular transverse minor diameter, long axis and anterolateral wall thickness to be determined. In calculations of volume from M mode echocardiography, the long axis is assumed to be twice as large as the short axis; the two dimensional studies proved that this is not always the case. Calculation of ventricular weight based on the "LD" formula increased the correlation coefficient from 0.595 to 0.736 and reduced the standard error of regression by 52 percent (Table II). A greater improvement in estimating ventricular weight was introduced by determining left ventricular wall thickness at different sites (Fig. 4). The correlation coefficient was increased from 0.736 to 0.900 when wall thickness was measured from these areas instead of calculated from the posterior wall alone.

In this regard, two dimensional echocardiography is particularly important in studying the different patterns of left ventricular hypertrophy in hypertension. Thus, early septal hypertrophy has been described in borderline hypertension, which contrasts with the more uniform hypertrophy in patients with long-standing hypertension.[22] However, a steep angle between the interventricular septum and the aorta can lead to oblique transection of the former by the echocardiographic beam, giving an erroneous impression of asymmetric septal hypertrophy.[23] This potential problem is avoided with two dimensional echocardiography.

Contrariwise, two dimensional echocardiography led to a more precise diagnosis of early hypertrophy in dogs with sustained significant hypertension at a stage when M mode echocardiography showed an apparently normal left ventricle. In these dogs, hypertrophy was mainly seen in the anterolateral left ventricular wall. Furthermore, two dimensional echocardiography revealed an increase in papillary muscle size, quite evident qualitatively but difficult to quantify precisely.

Implications: Our results suggest that evaluation of left ventricular changes in hypertension cannot depend on M mode echocardiography alone; a two dimensional view will avoid unwarranted and sometimes misleading assumptions. Cardiac involvement in hypertension can assume many forms.[1,4] Our model may help determine its multiple aspects, the rate of development of hypertrophy and particularly the possibility and consequences of its reversal by specific therapy.

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Cardiac Hypertrophy: Its Characteristics As a Growth Process

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The causal relation between cardiac function and growth is analyzed in this review article. Three different levels of development are discussed: cytodifferentiation, embryogenesis and postnatal development. The earliest stage of cardiac morphogenesis, that is, the appearance of cell-specific proteins and of spontaneous contractions, appears to be independent of hemodynamic forces. Also, the first major morphologic transformation of the primitive heart, looping, is the intrinsic property of the heart itself. However, at any later stage of life, hemodynamic function in both health and disease is closely coupled to cardiac growth.

The growth of the heart and circulatory requirements of the organism are interrelated from the earliest stage of ontogeny. As a result, the size of the adult heart closely matches the hemodynamic requirement typical of the environmental adaptation of a given animal.[1] The greatest ratios of heart to body size are found in animals whose survival depends on strenuous and prolonged physical exertion. Moreover, breeding for speed, as in the case of the greyhound or thoroughbred horse, leads to heart to body weight ratios that, even in the absence of training, exceed values found in mongrel animals. Although these examples demonstrate the relation between organ size and functional requirements, very little is known about the link between physical activity and the growth process.

In this review, we analyze the causal relation between changing cardiac function and growth at the cell level. Eventually, we want to know the extent to which cardiac morphogenesis is genetically programmed and the developmental stage and extent to which cardiac development and growth are modulated by epigenetic factors such as force and rate of contraction. Three different levels of cardiac development will be discussed: (1) cytodifferentiation, (2) embryogenesis, and (3) postnatal development.

Differentiation of Heart Cells

The scheme of cell differentiation leading to histogenesis of cardiac tissue is shown in Figure 1. The myogenic cells of the developing vertebrate heart are derived from splanchnic mesoderm[2] Because of experimental convenience, the earliest stages of cardiac development have been studied most thoroughly in the chicken. However, a similar description applies to mammals and to other amniotic embryos.[3]

During the first 30 hours of incubation of the fertilized egg, the myogenic cells appear rounded or spindle-shaped. The structure and abundance of various cell organelles are those typical of any undifferentiated cell. Although no muscle-specific structures are present at this stage, all of the cells will eventually acquire myofibrils. At this stage, the cells are referred to by different investigators as myoblasts or presumptive myocytes. During the subsequent 6 hours, the myoblasts begin to synthesize cell-specific proteins such as myosin and actin, and as a

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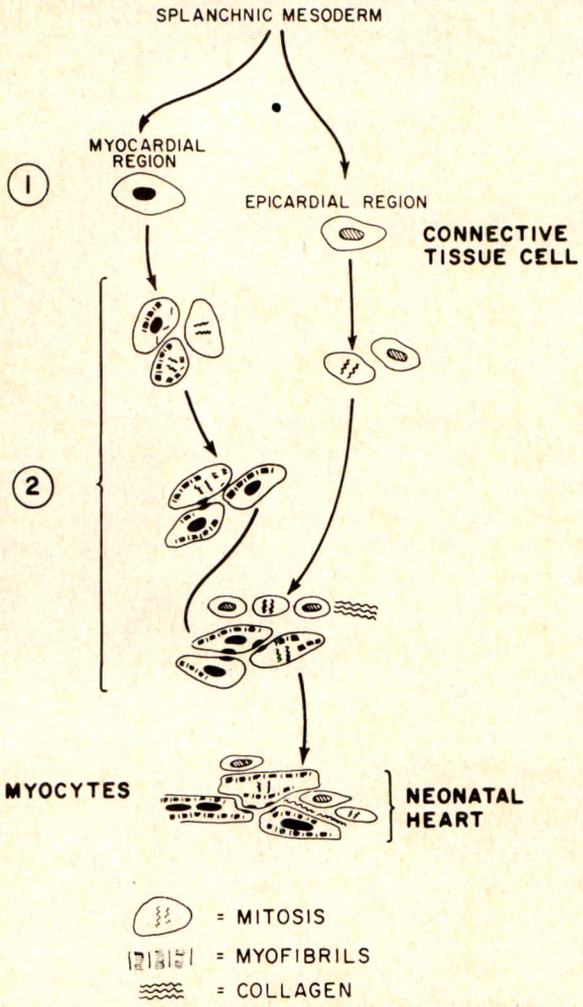

FIGURE 1. Scheme of myocardial development. ① indicates precardiac cells that do not exhibit the cardiac muscle cell phenotype (called either myoblasts or presumptive myocytes). ② indicates overtly differentiated muscle cells, that is, those that contain muscle specific proteins (called developing myocytes). The "connective tissue cells" represent a broad category of cells other than myoctes in this scheme.

consequence the first thick and thin filaments appear within their cytoplasm. (These cells are now referred to as developing myocytes.) At about 30 hours of incubation, the first contractions can be detected. Because the circulatory system has not yet developed, it is apparent that the earliest stage of cardiac morphogenesis occurs independent of hemodynamic forces. This conclusion is strengthened by the finding that an identical sequence of events occurs when cardiac cells are grown in culture.[4]

Embryogenesis

Process of looping: As the cardiac myocytes develop, the myofilaments become more abundant and demonstrate greater orientation, and by about 35 hours they begin to resemble myofibrils. The continuing formation of myofibrils is correlated with changes in cell shape. As a consequence, the bilaterally symmetric heart is transformed into an asymmetric C-shaped structure; this process is referred to as looping.[5] Although this morphologic change coincides with the onset of contractions, the hemodynamic forces were clearly shown not to be the morphogenetic factors that trigger looping. When the heartbeat, which is already present at this stage of normal embryogenesis, is prevented by placing the embryo explant into a medium containing a high concentration of potassium ions, the progression of looping remains similar to that seen in vivo.[6] Several lines of evidence obtained by Manasek et al.[7] indicate that looping requires a critical mass of myofibrils. First, it was shown that looping does not occur when myofibrillar assembly is prevented by cytochalasin B, or when either synthesis of total proteins is inhibited by cycloheximide or synthesis of contractile proteins is preferentially blocked by bromodeoxyuridine. It thus appears that both the information required for synthesis of cell-specific proteins and the forces responsible for the first major morphologic transformation of the primitive heart are intrinsic properties of the heart itself.

Postlooping stage: At the looping stage, the heart consists of a myocardium composed of a pure population of developing myocytes. The endocardium is still a simple endothelium, and no epicardium, coronary vessels or nerves are present. After looping, however, cardiac morphogenesis becomes a progressively more complex process. During this period, a variety of nonmuscle cells invade the myocardium, which gradually becomes composed of heterogeneous cell populations. In the 7 day old chick embryo, for example, in addition to myocytes, the following types of cells can be distinguished: vascular endothelial and smooth muscle cells, epithelial and mesenchymal cells of the epicardium, nerve cells, blood cells including phagocytes, and endothelial fibroblasts. The nonmuscle cells proliferate rapidly so that in the heart of the adult rat[8,9] they outnumber muscle cells three to one.

Another change in the myocardium that occurs after looping is that the myofilaments eventually form a substantial fraction of the cell volume. As a consequence, at a certain point of development, the cells lose their plasticity and cannot change their shape as readily as they could during looping. The morphologic transformations in the developing heart from this state onward become much more complex and are carried out mainly by two processes: differential growth and cell death.

Differential regional growth: The principal feature of cardiac growth during the embryonic period is a combination of cell proliferation (hyperplasia) and cell enlargement (hypertrophy). Both myoblasts and developing myocytes divide mitotically. In contrast to skeletal muscle, however, the synthesis of deoxyribonucleic acid (DNA) and that of cell-specific proteins are not mutually exclusive processes in cardiac myocytes. Cinematographic recordings of cultured embryonic heart muscle cells, for example, have clearly shown actively contracting cells in the process of division.[10] At first, the frequency of mitoses is high; however, as de-

velopment progresses, especially during the late gestation period, the number of dividing cells decreases and the enlargement of existing myocytes becomes the major mode of cardiac growth.

Myocardial cell death in the developing heart: In addition to preferential regional growth, death of myocardial cells has been implicated in morphologic transformations of the developing heart. Degeneration and death of cells are fairly common phenomena and accompany normal ontogeny in many tissues.[11] The ultrastructural features of degenerative changes in the myocardial cells likewise are similar to those in other tissues.[12] As degeneration proceeds, the typical spindle or cylindrical shape of myocytes is lost and the cells gradually become rounded. The loss of shape is accompanied by the loss of normal myofibrillar architecture. Moreover, during the process of rounding, the intracellular junctions become disrupted, and the dead cells are eventually moved out into the intercellular space. Once the cells are separated from the surrounding normal tissue, their degradation proceeds by the usual pathway within the phagocytes. There is general agreement among investigators about the universal occurrence of cell death. However, its frequency and distribution in various regions of the developing heart have not yet been causally related to the observed changes in cardiac shape.

Role of hemodynamic factors: The available experimental evidence, mostly obtained in studies of cardiac malformations, indicates that in contrast to early morphogenesis, cardiac embryogenesis after looping is affected by hemodynamic factors. For example, the decreased inflow of blood created by occlusion of the atrioventricular (A-V) canal was shown in the chick embryo to result in an abnormally small left atrium and ventricle (referred to as hypoplasia) and in simultaneous enlargement of the right heart chambers.[13,14] Somewhat different results were obtained when the blood flow was modified by selective occlusion of various aortic arches.[15] As a result of such intervention, the size of the left atrium was diminished as in occlusion of the A-V canal, but in addition a marked narrowing of the aortic arch was present. However, the left ventricle did not enlarge as would be expected after aortic coarctation; instead, its growth was suppressed and a variety of ventricular septal defects were observed.

In addition to its effect on cardiac growth, manipulation of intracardial blood flow alters the topography and frequency of cell death in the developing chick myocardium.[16] Despite rather limited information, the foregoing results indicate that after looping, the hemodynamic factors are causally related to growth and development of the heart under some circumstances.

Postnatal Development

During the late embryonic period, the mitotic activity of cardiac myocytes declines rapidly; consequently, at birth only about 2 percent of the rat heart cells are dividing. During the neonatal period, mitotic activity continues to decline and, at about 2 months of age, mitoses in the rat heart are noted only infrequently, if at all. Nevertheless, the number of myocytes in the rat heart doubles during the first 3 to 4 weeks of life.[17–19]

Factors influencing proliferation of cardiac myocytes: Two points concerning the proliferation of cardiac myocytes must be emphasized. First, the exact timing of the development mentioned applies to the rat only. The maturity and size of the heart relative to body weight vary among species depending on their life-style. The heart size at birth of animals such as sheep, goats and cattle, whose survival depends on their ability to run soon after birth, is about one-third the adult size. In contrast, the heart of rabbits, dogs or cats is only about one-sixth the adult size.[1] Second, the rapid decrease in mitotic activity during the late embryonic and early neonatal periods is by no means typical only of cardiac myocytes. A similar decline occurs in all cells except those of renewing tissues such as the epidermis, mucosal epithelium of the gut, and blood cells. In contrast to most other cells, however, the myocytes of the adult myocardium have never been unequivocally shown to resume mitosis secondary to either injury[19] or induced growth.[8,9,21,25]

Hemodynamic function and cardiac growth: compensatory hypertrophy: In the postnatal period, the importance of hemodynamic function in the regulation of cardiac growth is clearly documented by several lines of evidence, including comparison of the growth rates of the left and right ventricles. During prenatal life, the work load of both ventricles is equal as is their size.[23] However, closure of the foramen ovale after birth results in rapid growth of the left ventricle whereas the decreased function of the right ventricle is accompanied by a drastic reduction in its rate of growth.[24]

Further evidence comes from the common observation that an increase in hemodynamic load on the heart, due either to pathologic changes in the cardiovascular system or to increased physiologic activity, promptly induces cardiac growth. The resulting ratios of heart weight to body weight exceed values typical for normal animals of a given species. The observed growth, commonly referred to as compensatory hypertrophy, can be viewed as an adaptive process because it allows the individual to survive. The term hypertrophy in this case is understood as enlargement of the entire organ rather than of its constituent cells as is implied in the definition of hypertrophy used by cell biologists. The cell features of compensatory cardiac hypertrophy vary depending on the age of the animal at the time of onset of the work overload. Thus, if the growth stimulus is applied during the period when mitoses are still present, that is, during the first 3 to 4 postnatal weeks, autoradiographic[17–22,25,26] and histometric[27] data indicate that accelerated nuclear divisions accompanying cardiac enlargement. In contrast, similar experimental procedures applied to adult animals do not lead to increased DNA synthesis in cardiac myocytes,[8,9,20–22] and accordingly the observed cardiac enlargement can be explained by an increase in the volume of existing myocytes. How-

ever, in human heart disease, if there is extreme enlargement, cell hypertrophy is supplemented by the addition of new muscle cells.[28]

An example of the compensatory hypertrophy produced by constriction of the ascending aorta of the mature rat is shown in Figure 2. The adaptive nature of the growth response is best shown if the weight of the hypertrophic heart is superimposed on the growth curve of the normal myocardium. After the operation, the heart enlarges very rapidly, approximately in exponential fashion, until the compensatory stage is reached, when the new hemodynamic load is matched by the enlarged myocardium. When the constricting band is removed, heart size returns to typically normal values.[29] The rate of regression of cardiac hypertrophy is as rapid as its development.

Factors regulating processes of cardiac growth: Although similar correlations between hemodynamic load and cardiac growth have been observed in a great variety of experimental models, very little is known about the factors that regulate the processes of growth. One very important question, recently addressed by Hollenberg[30] and Rakusan[31] and their associates, is whether the number of cell divisions of cardiac myocytes is genetically programmed or whether it can be modified in normal animals by factors that affect body growth. Both groups of investigators manipulated the rate of body growth by adjusting the number of newborn animals per litter. The smaller the litter, the greater was the rate of postnatal growth. The cell proliferation was assessed by two methods. First, it was determined histometrically from measured cell diameters, the total volume of the sample and its fraction occupied by myocytes, and assumed length to width ratios.[31] Second, the rate of nuclear proliferation was derived from the radioautographically determined decrease in the density of nuclear labeling with ^{3}H-thymidine.[30] (However, not every nuclear division necessarily leads to cell division. Because it is well known that the number of cells with more than one nucleus increases after birth,[32] the second method provides information only about the nuclear activity and not about the total number of muscle cells.) In both cases, the data are consistent with the interpretation that the rate of myocyte proliferation is increased when body growth is enhanced during the weaning period. On the basis of this evidence, a genetically programmed finite number of mitotic divisions in the myocardium does not exist.

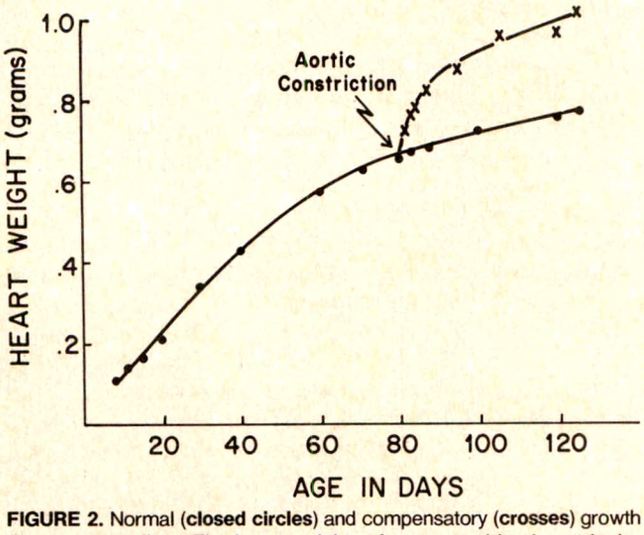

FIGURE 2. Normal (**closed circles**) and compensatory (**crosses**) growth of rat myocardium. The heart weight refers to combined ventricular weight of Sprague-Dawley female rats. To induce cardiac hypertrophy the ascending aorta was constricted to approximately 30 percent of the original diameter of the lumen by means of a hemostat clip.

Regulation of DNA synthesis and cardiac growth: Our knowledge of the molecular mechanisms responsible for the regulation of DNA synthesis and growth in general is still limited. It has been established that the decline in mitotic activity correlates in time with the loss of activity of both DNA polymerase-α[33] and thymidine kinase.[34] However, most measurements of enzyme activity reported thus far have only limited value because no distinction was made between nuclei of muscle cells and those of nonmuscle cells. Recently, a procedure was developed that allows separation of muscle and nonmuscle cells.[35] Using this technique, we demonstrated that muscle cell DNA polymerase-α which normally decreases to low levels during the neonatal period, is activated when cardiac enlargement is induced in 25 day old rats by aortic constriction.[36]

In several studies, attempts were made to identify the factors regulating DNA replication. For example, adenosine diphosphate (ADP) ribosylation of chromosomal proteins* was reported to be inversely related to the rate of DNA synthesis measured in mixed nuclei of growing hearts.[37] The appearance of functional adrenergic innervation was also implicated in the control of DNA replication, with noradrenalin and cyclic adenosine monophosphate (cAMP) acting as the chemical modulators.[38] In another study, radioautographic assessment of DNA synthesis in neonatal hearts suggested that a low oxygen environment similar to that found in utero increases the incorporation of ^{3}H-thymidine into muscle nuclei.[39] It is likely that the low partial pressure of oxygen reduces the synthesis of poly(ADP)-ribose, which has been shown in a variety of experimental systems[40] to act as an inhibitor of DNA synthesis. Equally little is known about the factors that control gene expression. The acidic nonhistone proteins have frequently been implicated in regulation of the transcription process. One possibility is that the activity of acidic proteins is modulated by phosphorylation catalyzed by cyclic AMP-dependent nuclear protein kinase.[41,42] Another possibility is that the chromatin proteins are covalently modified by ADP ribose by way of an enzymatic transfer from poly(ADP)-ribose. ADP ribosylation has been shown to accompany repression of chromatin activity.[43] Moreover, polyamines, which

* Sequential transfer of ADP ribosome moiety of NAD to-chromosomal protein.

are present in elevated amounts in growing organs including the hypertrophic heart,[44] serve as a trap for an intermediate in the ADP-ribosylation reaction.

Molecular aspects of cardiac growth and hypertrophy: The experiments described are examples of attempts to decipher the still elusive mechanisms coupling the physical activity of an organ with its rate of growth. At present, our knowledge is still too limited to allow us to formulate a unifying hypothesis for the control of cell growth. However, in addition to the regulation of DNA synthesis, gene expression is certainly modulated also at other levels. This modulation involves, for example, the amount or activity, or both, of ribonucleic acid (RNA) polymerase, a variety of humoral factors including norepinephrine,[45] and muscle growth-stimulating RNA.[46] A recent report[47] suggests that extracts from hypertrophic heart enhance the translational activity of RNA prepared from the normal heart. Finally, the rate of growth might also be controlled by changes in the rate of protein degradation. The control of gene expression at the levels mentioned in our study is discussed in more detail in our recent review of the molecular aspects of cardiac hypertrophy.[48]

Thus it appears from a review of our currently available information concerning the growth characteristics of the myocardium that the first steps in its development are independent of its function. At any later stage of life, however, the hemodynamic function both in health and in disease is closely coupled to cardiac growth. The transition between physiologic and pathologic growth still remains to be elucidated.

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Functional Significance of Altered Myosin Adenosine Triphosphatase Activity in Enlarged Hearts

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Enlarged hearts secondary to significant pressure overload have a depressed myosin adenosine triphosphatase (ATPase) activity. With mild stress the ATPase activity may be normal or slightly elevated. Enlargement of the heart after exercise or thyroid stress results in an increased ATPase activity. Rapid myothermal techniques, in particular measurements of tension-dependent heat, were used to evaluate: (1) the relation of in vitro measurements of actin-activated ATPase activity to the in vivo behavior of myosin, and (2) the contribution of these changes to the economy of tension development and the time course of crossbridge cycling. Experiments were carried out in animals whose hearts were enlarged secondary to pressure overload (by pulmonary arterial banding) or thyrotoxic stress. In vitro actin-activated ATPase activity levels were 70 and 175 percent of normal for the pressure-overloaded and thyrotoxic hearts, respectively, while the tension-dependent heat per unit tension for the same preparations was, respectively, 78 and 154 percent of normal. Thus there is a reasonable correlation between the in vivo and in vitro measurements of contractile protein ATPase activity, which indicates that the economy of tension development is inversely related to tension-dependent heat per unit tension or actin-activated myosin ATPase activity. Analysis of these data in terms of the kinetics of ATPase activity, crossbridge behavior and tension development leads to the conclusion that in pressure overload hypertrophy the adaptation involves a decrease in the crossbridge cycling rate, an increase in crossbridge off-time and an increase in the on-time of the crossbridge. For thyrotoxic hypertrophy the adaptation involves an increase in the cycling rate, a decrease in the off-time and a decrease in the on-time. The former is adapted for slow, economical tension development and the latter for rapid, less economical tension development.

Alpert and Gordon[1] reported that myofibrillar adenosine triphosphatase (ATPase) activity was depressed in samples of ventricular myocardium from patients who died in cardiac failure with hearts hypertrophied secondary to hypertensive heart disease (Fig. 1). This study raised the question of the relation between the myofibrillar ATPase activity and myocardial function in enlarged hearts.

Subsequent refinements in the techniques of evaluating the myocardial contractile protein ATPase activity involve studies on purified myosin or proteolytic fragments of purified myosin activated by actin or calcium ion. A large number of investigators[2–9] have observed a significant reduction in actin- or calcium-activated myosin ATPase activity from hearts hypertrophied secondary to pressure overload. In contrast to this depression, after exercise there is an increase in myosin ATPase activity that is correlated with the duration of the training.[10] Similarly, when the heart enlarges in response to a thyroid stress there also is an

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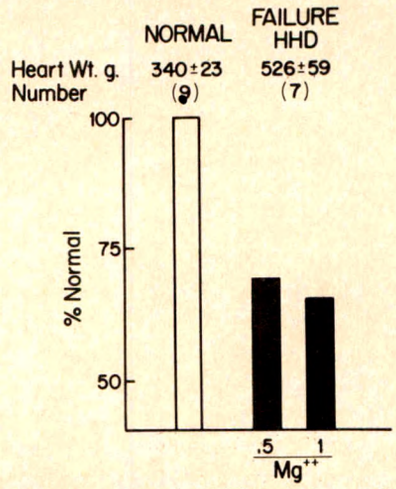

FIGURE 1. Myofibrillar adenosine triphosphatase activity in normal and failing hearts. Assays were carried out at pH 7.1. The final millimolar concentrations of adenosine triphosphate, potassium chloride and Tris buffer were 5, 100 and 10, respectively. The millimolar concentration of Mg^{++} is the same for the control group as that indicated for the experimental hearts. The failing hearts were from a group of patients, ranging in age from 49 and 85 years, who died from congestive heart failure after hypertensive heart disease (HHD). The normal hearts were from subjects ranging in age from 25 to 46 years who died from traumatic injury.[1]

increase in myosin ATPase activity.[11–17] In some studies of myocardial hypertrophy secondary to pressure overload, no change or an increase in myosin ATPase activity was observed.[18–23] Thus hearts enlarged as a result of pressure overload have a depressed myosin ATPase level if the stress is severe enough. With mild stress the myosin ATPase may be normal or slightly increased. Enlargement of the heart after exercise or thyroid stress results in increased myosin ATPase activity.

It is important to ascertain the relation of in vitro measurements of actin-activated myosin ATPase activity in the various enlarged heart preparations to the intracellular behavior of the myosin, where it is organized into thick filaments and associated with actin in a hexagonal pattern. Furthermore, the effect of these alterations in myosin on the energetics of tension development should provide information relating to the crossbridge cycling pattern during tension development.

The plan in these experiments is to use two animal models, those of pressure overload and thyrotoxic myocardial hypertrophy, where specific qualitative differences in mechanics and myosin ATPase activity are known to exist (Table I). In each of these models the intracellular behavior of the myosin is evaluated by means of rapid myothermal methods. With these techniques the initial heat can be measured and partitioned into a tension-dependent and a tension-independent portion. The tension-dependent heat is a measure of myosin crossbridge cycling and adenosine triphosphate (ATP) splitting. It thus should provide information about myosin ATPase activity and energetics during tension development in the intact heart muscle cell.

TABLE I

Changes Relative to Normal Values in Pressure Overload and Thyrotoxic Hypertrophy

	Pressure Overload Hypertrophy	Thyrotoxic Hypertrophy
Peak twitch (isometric)	No change or slight decrease	Decrease
Velocity (unloaded shortening)	Decrease	Increase
Time to peak tension	Increase	Decrease
Myosin ATPase	Decrease	Increase

Methods

Animal models: All experiments were performed on heart tissue from male albino rabbits. Pressure overload hypertrophy was induced by placing a spiral metal constrictor around the proximal pulmonary artery by means of the procedure previously described.[24] Measurements were made on these hearts 4 to 6 weeks postoperatively. Thyrotoxic hypertrophy was induced by 14 daily injections of L-thyroxine* (0.2 mg/kg); the rabbits were then killed and the hearts used in the manner to be described.

Myosin and actin isolation and ATPase measurements: Myosin was prepared according to the method of Shiverick et al.,[25] which was developed for the purification of myosin from small amounts of cardiac tissue. Actin was extracted by the method of Rees and Young[26] from an acetone powder of the back and leg muscles of rabbits.[27] Actin-activated myosin ATPase activity was assayed as previously described.[7]

Myothermal and force measurements: Right ventricular papillary muscles were excised and mounted on the planar vacuum-deposited thermopiles as previously described.[28] The tendinous end of the muscle was anchored to a stationary hook while the cut end was attached to an isometric force transducer.[29] A tether ensures close contact of the muscle with the thermopile elements. The thermopile has low thermal capacity, high sensitivity and low electrical resistance, so that it can be matched with a Kipp galvanometer recording system. The frequency response of the entire system is 60 hertz and the cumulative drift 0.14 mcal/hour. When a 5 kilohertz subthreshold sine wave was applied to the papillary muscle there was a 6.5 msec delay between the current onset and a detectable temperature change. When the muscle was stimulated, the earliest detectable temperature change occurred 19 to 20 msec after the stimulus. Thus the thermal delays are of small enough magnitude so that initial heat measurements associated with each twitch can be made with assurance. The entire myothermal assembly was placed in a 70 liter constant temperature bath where equilibration in Krebs-Ringer solution was carried out at 21° C for 2 hours. The muscle was stimulated at 0.2 hertz, and the experiments were accepted only if muscle heat and tension performance were stable over the entire experimental period and twitch tension was at least four times greater than resting tension.

Initial heat and tension-dependent heat measurements: A record of the steady state temperature change of a stimu-

* L-thyroxine was kindly supplied by Flint Laboratories, Deerfield, Illinois.

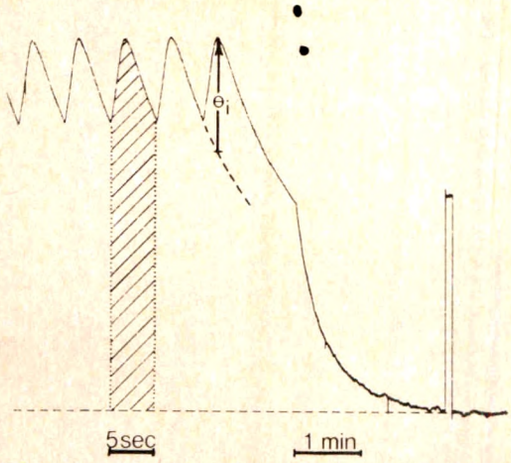

FIGURE 2. Temperature change during steady state stimulation of right ventricular papillary muscle. θ_i represents temperature change associated with initial heat liberation (see text for extrapolation procedure). The **cross-hatched area** represents total heat liberated during a twitch. The slanted line (**dashes**) is the resting temperature (see text).

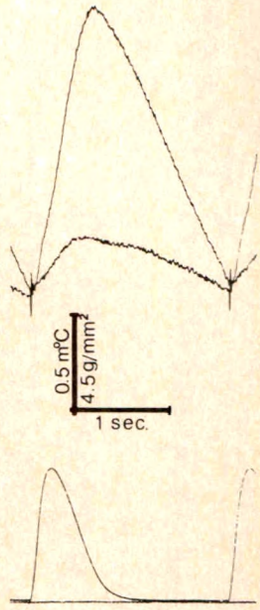

FIGURE 3. Temperature change (**upper record**) and force development (**lower record**) of an isolated papillary muscle stimulated at 0.2 hertz. The large temperature excursion (**upper tracing, upper record**) represents the initial heat production during the development of isometric force (**upper tracing, lower record**). Initial heat is the sum of tension-dependent heat and tension-independent heat. When the muscle is incubated in 2.5 × N hyperosmotic Krebs solution, a triggerable heat output remains (**lower tracing, upper record**). The heat output under these conditions is the tension-independent heat. The tension dependent heat is the difference between the initial heat and the tension-independent heat.

lated papillary muscle is shown in Figure 2. The temperature of the muscle is a function of resting heat, initial heat and recovery heat. The temperature change associated with the initial heat liberation was corrected for heat loss by the extrapolation procedure shown by the dashed line in Figure 2. This trace was obtained by translating the cool-off curve that occurs on cessation of stimulation to permit a valid extrapolation of earlier responses. The corrected temperature change (θ_i) was converted to the corresponding heat evolution by multiplication with the effective heat capacity of the muscle plus adhering Krebs solution determined as previously described.[28] The initial heat consists of tension-dependent and tension-independent heat. Tension-independent heat was obtained by measuring the triggerable heat output when tension was eliminated by incubating the muscle in 2.5 × N hyperosmotic mannitol-Krebs solution (Fig. 3). The tension-dependent heat, which represents crossbridge cycling during tension development, is the difference between initial heat and tension-independent heat.

Results

General findings: The right ventircular heart weight/body weight ratio increased by 197 percent and 213 percent, respectively, in thyrotoxic and pressure overload hypertrophy (Table II). There was no change in the papillary muscle cross-sectional area for the thyrotoxic muscle; that of the pressure-overloaded preparation was 178 percent of normal. The dry/wet weight ratios for papillary muscles were unchanged for the pressure overload and thyrotoxic preparations. The dry/wet weight ratio for the liver was unchanged for the thyrotoxic and 116 percent of normal for the pressure-overloaded preparations.

Myosin ATPase activity: Actin-activated myosin ATPase activity was 175 percent ($P < 0.001$) and 70 percent ($P < 0.05$) of normal in the thyrotoxic and pressure-overloaded preparations, respectively. There was no change in the (K^+) EDTA-activated ATPase activity.

Mechanical and thermal measurements: Peak isometric twitch tension was 5.8 ± 0.3 standard error of the mean g/mm^2 for the control muscles. The thyrotoxic and pressure overload preparations had twitch tensions of 72 percent ($P < 0.05$) and 84 percent (not significant) of the control values, respectively. Tension-dependent heat measurements were made in four series of control, three series of pressure-overloaded and one series of thyrotoxic preparations. Generally, tension-dependent heat was high in the thyrotoxic and low in the pressure-overloaded preparations (Table III). The tension-dependent heat correlated with actin-activated ATPase activity (Fig. 4).

Discussion

Constriction of the pulmonary artery or thyrotoxic stress dramatically increases the power requirements

TABLE II

Thyrotoxic and Pressure Overload Hypertrophy

	RV/Body Weight (g/kg)	Cross-Sectional Area of RV Papillary Muscle (mm^2)	Dry/Wet Weight	
			Papillary Muscle	Liver
Normal	0.31 ± 0.01	0.59 ± 0.04	0.23 ± 0.006	0.28 ± 0.01
Thyrotoxic hypertrophy	0.61 ± 0.02	0.66 ± 0.06	0.24 ± 0.005	0.25 ± 0.01
Pressure overload	0.66 ± 0.09	1.05 ± 0.11	0.24 ± 0.005	0.32 ± 0.02
Thyrotoxic hypertrophy/normal	1.97 ($P < 0.002$)	1.11 (NS)	1.06 (NS)	0.91 (NS)
Pressure overload hypertrophy/normal	2.13 ($P < 0.001$)	1.78 ($P < 0.001$)	1.04 (NS)	1.16 ($P < 0.02$)

NS = not significant; P = probability; RV = right ventricular.

TABLE III

Tension-Dependent Heat per Unit Tension (μcal/g cm)*

Series	no.	Control	Thyrotoxic Hypertrophy	Pressure Overload Hypertrophy
I	5	2.86 ± 0.30		1.72 ± 0.36
II	10	1.64 ± 0.22		1.63 ± 0.22
III	5	2.62 ± 0.17		2.26 ± 0.35
IV	8	2.08 ± 0.21	3.65 ± 0.18	
Mean		2.15	3.65	1.81

* [Heat (cal)/muscle mass (g)] ÷ [twitch tension (g) × muscle length (cm)/muscle mass (g)] *or* (Hc/g) ÷ ($P_{TW}l_o$/M).

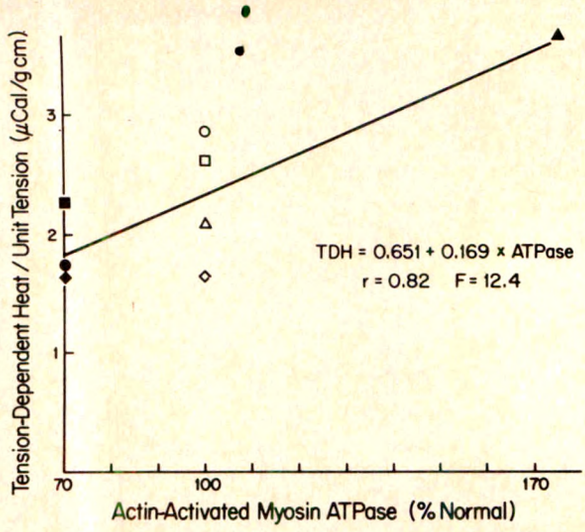

FIGURE 4. Relation between actin-activated myosin adenosine triphosphatase (ATPase) and tension-dependent heat (TDH) per unit tension. **Open symbols** represent the control and **closed symbols** the experimental series. Series I, II, III and IV (Table III) are represented by the following symbols, respectively: O—●; ♦ ◊; ■ □; and ▲ △.

placed on the right ventricle. The hypertrophy that results from prolonged stress permits the heart to meet the additional demands placed on it. However, the changes that occur after the development of hypertrophy are not the result of adding on a number of identically functioning subunits. There are significant changes at the molecular level that contribute to the quality of the adaptation as well as to its limitations. Actin-activated myosin ATPase is 70% of normal in the pressure-overloaded and 175 percent of normal in the thyrotoxic preparations. Thus, there are oppositely directed fundamental alterations in the contractile proteins in the two types of enlarged heart. It was the goal of these experiments to evaluate the functional significance of this alteration. High-speed myothermal measurements permit an analysis of the energetic contribution of altered proteins to force development.

Myosin ATPase correlated with tension-dependent heat: The correlation between actin-activated myosin ATPase and the tension-dependent heat (Fig. 4) lends support to the hypothesis that in vitro measurements of myosin ATPase activity reflect the in vivo behavior of the myosin during isometric force development. This is consistent with the correlation of tension-dependent heat rate, maximal speed of contraction and myosin ATPase activity found in fast and slow twitch muscles in the rat[30] and the chicken.[31]

The change in myosin ATPase activity (increase in thyrotoxic hypertrophy, decrease in pressure overload) is known to correlate with unloaded shortening velocity.[32–34] Thermal measurements were made to evaluate the possibility that changes in myosin ATPase activity alter crossbridge kinetics in a manner that affects isometric tension as well as mechanical rate of shortening velocity (V_{max}). From measurements of fast and slow muscles in the rat[30] one would predict a two-fold change in tension-dependent heat for each one-fold change in ATPase activity. This did not occur. In fact there was a slightly smaller depression in tension-dependent heat than in myosin ATPase activity for the pressure-overloaded preparations (22 versus 30 percent) and a somewhat smaller increase in tension-dependent heat than in myosin ATPase activity for the thyrotoxic preparations (54 versus 75 percent).

Myosin crossbridge cycling and tension development: It is useful to examine these data in terms of an enzyme kinetic analysis of crossbridge cycling and tension development (Fig. 5).[35] Force and work are produced when myosin crossbridges propel the thin filaments along the thick filaments toward the center of each sarcomere. Each time a globular head of a nonrefractory myosin crossbridge makes contact with an actin monomer in the thin filament, it undergoes a "rowing" action that generates the sliding force between thin and thick filaments. On completion of its propelling stroke, the myosin crossbridge binds one ATP molecule, dissociating it from the actin filament and allowing it to hydrolyze the bound ATP and become available to repeat the cycle.

Although each cycle of a particular bridge produces only a momentary impulse of force, the summation of these impulses from millions of randomly cycling crossbridges gives rise to a steady force or shortening at the ends of the muscle. For a given number of cycling crossbridges the average value of this force is proportional to the amplitude of the impulse (that is, the strength of the bridge, S), its duration (the on-time, τ) and the rate of crossbridge cycling, f (Table IV, Fig. 6).

The biochemical reactions giving rise to each step in the crossbridge cycle (Fig. 5): *The cycle consists of the following steps:* (1) ATP is rapidly hydrolyzed on the dissociated myosin (M) head (M^* ATP → M^{**} $ADPP_i$), leaving it in an energized but refractory state; (2) a slow, rate-limiting, conformational change occurs in the myosin, transforming it from the refractory to the nonrefractory state ($M^{**}ADPP_i \rightarrow M^{\ddagger}ADPP_i$); (3) the nonrefractory crossbridge connects to the actin (A) filament ($M^{\ddagger}ADPP_i + A \rightarrow AM^{\ddagger}ADPP_i$); (4) the contact angle between the crossbridge head and the actin filament changes from 90° to 45°, stretching the flexible portion of the bridge and generating tension ($AM^{\ddagger}ADPP_i \rightarrow AM\ ADPP_i$); (5) the subsequent loss of

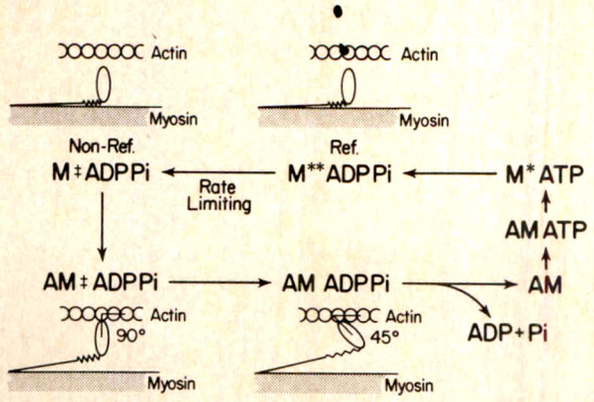

FIGURE 5. Schematic diagram (see text) of actin-activated myosin (M) kinetics and crossbridge behavior. A = actin; ADP = adenosine diphosphate; ATP = adenosine triphosphate; M = myosin; Pi = inorganic phosphate. (Redrawn from Eisenberg and Hill.[35])

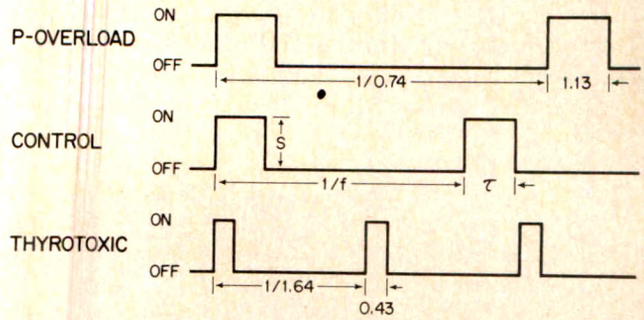

FIGURE 6. The crossbridge on-off cycle during activation for pressure (P) overload and thyrotoxic preparations. The assumptions underlying the cycling profile are presented in the text and in Table IV. Each tracing represents the time course of crossbridge connection to actin "on" and dissociation from actin "off" for a control, pressure-overloaded and thyrotoxic crossbridge. f = crossbridge cycling rate; S = crossbridge strength; τ = crossbridge "on" time.

hydrolysis products (ADP + P_i) and binding of an ATP molecule to AM causes a rapid dissociation of the crossbridge and completes the cycle (AM + ATP → AMATP → A + M*ATP).

The main features of this scheme are that a single cycle of the activated contractile system exists in two distinct states, where the actin and myosin are dissociated or associated. In the dissociated or "off" state, the rate-limiting step between M**ADPP_i and M‡ADPP_i probably plays the major role in determining the overall cycling rate (f) and, hence, myosin ATPase and mechanical V_{max}. In the associated or "on" state, force is generated when the crossbridge head rotates from the 90° to the 45° position, stretching the compliant elements in the myosin molecule during the on-time. This corresponds to the conformational states AM‡ADPP_i and AM ADPP_i.[35] This two state cycle enables the rate of energy liberation (that is, rate of ATP hydrolysis, mechanical V_{max} and rate of tension-dependent heat liberation) to be controlled independently of force production. Changes in force that would accompany increases or decreases in cycling rate that result from a change in the rate-limiting step (M**ADPP_i → M‡ADPP_i) can be compensated by oppositely directed changes in crossbridge on-time (AM‡ADPP_i → AM ADPP_i). Furthermore, the economy of force production (i.e, tension-dependent heat per unit tension) is also controlled by the time spent by the crossbridge in the "on" (45°) state relative to the cycle time, since each crossbridge cycle is obligated to hydrolyze one ATP molecule and liberate the bond energy as mechanical work and heat in the same proportion as the ratio of crossbridge on-time to cycle time.

Energetics of tension development analyzed in terms of the on-time and the cycling rate (Table IV): As a first approach to quantification of chemomechanical transduction we will consider a greatly simplified model for illustrative purposes. Assume that the tension-dependent heat or the actin-activated myosin ATPase is a good measure of the cycling rate.

TABLE IV

Data and Assumptions for Calculating Crossbridge On-Time

Thyrotoxic Data	T/C*	Hypothesis	T/C
Myosin ATPase	= 1.75	Crossbridge cycling rate(f)	= 1.64
Tension dependent heat/unit tension	= 1.54		
Peak twitch tension	= 0.71	$P^{\dagger}_{TW} = f \times \tau \times S$	
		$0.71 = 1.64 \times \tau \times S$	
		Assume crossbridge strength(s)	= 1
		then crossbridge on-time (τ)	= 0.43
Pressure Overload Data	**P/C***	**Hypothesis**	**P/C**
Myosin ATPase	= 0.70	Crossbridge cycling rate (f)	= 0.74
Tension-dependent heat/unit tension	= 0.78		
Peak twitch tension	= 0.84	$P_{TW} = f \times \tau \times S$	
		$0.84 = 0.74 \times \tau \times S$	
		Assume crossbridge strength (S)	= 1
		then crossbridge on-time (τ)	= 1.13

* Values given as ratio of experimental (T or P) to control tissue (C).
† See text for logical basis of this relation.

Hence we take the mean of the hypertrophy-induced fractional change in heat and ATPase activity as the fractional change in crossbridge cycling rate. Further, the average force per bridge during one cycle equals the on-time (τ) divided by the cycle period (1/f) multiplied by the strength of the bridge (S), hence $P_{TW} = \tau \times f \times S$, where P_{TW} = twitch tension and f = cycling rate. If we assume that the crossbridge strength does not change (that is, the stiffness of the flexible portion of the myosin molecule and the extent of its rowing stroke) with hypertrophy, the pressure-overloaded preparation develops force more economically (that is, less tension-dependent heat per unit tension) by increasing the on-time by 13 percent and decreasing the cycling rate by 26 percent (Fig. 6). Conversely, the thyrotoxic preparation develops force less economically by increasing the cycling rate by 64 percent and decreasing the crossbridge on-time by 57 percent (Fig. 6). The pressure-overloaded hypertrophied heart is adapted for economical force development at slow rates,[36,37] whereas the hearts enlarged after thyrotoxic stress are adapted for rapid force development at low economy. The economy of force development is inversely related to the tension-dependent heat, which is a measure of the in vivo actin-activated myosin ATPase activity. The ability of the heart to alter the conformation of the myosin molecule synthesized in response to stress (pressure overload, thyrotoxic) provides the basis for one aspect of the adaptation that occurs. It is thought that the major structural change in the myosin molecule occurs in the vicinity of the fast-reacting first class sulfhydryl (SH_1) group.[6,7,14–16]

Implications: Rapid myothermal measurements may thus provide a link between the analysis of crossbridge behavior by rapid mechanical transient measurements of muscle cells and the in vivo analysis of rapid enzyme kinetics. Such correlations of high speed mechanical, myothermal and enzyme kinetic responses of the contractile apparatus are essential to provide data with which to test a more realistic model of crossbridge behavior, such as those of Eisenberg and Hill,[35] Huxley and Simmons,[38] and Podolsky and Nolan.[39]

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Collagen Synthesis in Development and Reversal of Cardiac Hypertrophy in Spontaneously Hypertensive Rats

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An alteration in the rate of collagen synthesis was observed in spontaneously hypertensive rats during evolution of hypertension. An increase in rate of synthesis of collagen and a parallel increase in collagen content were observed in 4–8 week and 24 week old hypertensive rats. In the 4 week old rats, blood pressure was normal or nearly normal, whereas in the 24 week old rats the arterial pressure was significantly elevated. Use of some antihypertensive drugs, namely, α-methyldopa, converting enzyme inhibitor and a combination of reserpine, hydrochlorothiazide and apresoline, prevented hypertension and the late increase in collagen synthesis that was observed in the 24 week old hypertensive rats. In these rats, prevention of hypertension also reversed myocardial hypertrophy and reduced collagen content of the myocardium. The alteration of myocardial collagen synthesis in spontaneously hypertensive rats is a complex process in which at least two phases can be observed. In the young rats, in which blood pressure is normal, the stimulus to increase in collagen may be a humoral factor or a hemodynamic alteration such as hyperkinetic circulation or it may be a genetic factor. In the older hypertensive rats hypertension seemed more important in altering collagen synthesis because antihypertensive therapy inhibited the rate of collagen synthesis and protected the heart from excess accumulation of collagen.

Hypertension is an important risk factor for cardiovascular disease in man, but its relation to the biochemical changes in the cardiovascular system is not well established. Wolinsky et al.[1,2] showed that lysosomal enzyme activity is increased in the aorta of rats with experimentally induced hypertension. They concluded that lysosomal enzymes may have a role in the development of the atherosclerotic plaque. Recently, investigators in several laboratories[3–5] reported that vascular collagen synthesis is greatly increased when arteriosclerosis is induced by chemical or mechanical damage to the arterial wall. Others[1,6] reported that the long-term effect of hypertension and arteriosclerosis was similar to that of vascular fibrosis. Freis et al.[7] reported that dilatation of the arterioles due to hypertension causes damage to elastic laminae and stimulates collagen synthesis.

We have reported an age-dependent increase in collagen content of the myocardium of spontaneously hypertensive rats. In the 3 and 24 week old rats, the collagen content was significantly elevated, whereas in 10–15 week old rats the content was the same as in the control rats. The rate of synthesis of collagen showed parallel changes.[8] The stimulus for increased collagen synthesis in the young or old spontaneously hypertensive rat is not known. Because arterial pressure had been normal in the 4 week old hypertensive rat, pressure is not likely to be a causal factor. In the older hypertensive rat, however, elevated blood pressure persisting for a long time may have a role in triggering collagen synthesis. The

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present study was conducted to evaluate the effect of long-standing hypertension on rate of collagen synthesis and collagen content in spontaneously hypertensive rats by preventing the development of hypertension by oral antihypertensive therapy.

Methods

Study groups: All spontaneously hypertensive rats used in this study were the Okamoto-Aoki strain obtained from Taconic Farm (Germantown, New York). The normotensive controls were age- and sex-matched Kyoto Wistar rats. Both normotensive and hypertensive rats were kept under the same conditions, properly housed and fed (Purina® Rat Chow). Arterial pressure was measured by using a tail cuff in a method similar to that described by Friedman and Freed.[9] In all experiments, rats were killed by decapitation and ventricles were cleaned as described previously.[10]

Collagen synthesis study: For the study of collagen synthesis, ventricles were homogenized in cold Krebs bicarbonate buffer, pH 7.5 (150 mg/ml). Ten μCi of Carbon-14 proline (New England Nuclear) was added and incubated under a mixture of 95 percent oxygen and 5 percent carbon dioxide for 3 hours at 37 °C with rapid shaking. Reaction was stopped by adding 0.1*N* HCl:ethanol (1:20) and washing was carried out three times with same acid ethanol, two times with ethanol ether (1:3), and finally with ether. Free proline in the combined supernatant was determined (both radiometrically and colorimetrically) by the method of Troll and Lindsley.[11]

The residue was homogenized in cold HEPES buffer (pH 7.4). The following concentrations were determined by taking a known aliquot: (1) Hydroxyproline concentration was determined after hydrolysis for 24 hours with 6*N* HCl; the method described by Bergman and Loxley[12] was used. (2) Total carbon-14 counts were determined before collagenase treatment. (3) A third aliquot was treated with chromatographically pure collagenase (Worthington Chemicals) and incubated for 4 hours at 37°C with continuous shaking. At the end of 4 hours, reaction was stopped by adding 5 percent TCA = 0.25 percent tannin, and washing was carried out to three times with 3 to 4 volumes of the same mixture, and centrifuged. The radioactivity of the precipitate was determined in a Packard scintillation counter. The supernate (collagen) was dialyzed overnight at 4°C, evaporated to dryness, and hydrolyzed by adding 6*N* HCl at 110° for 24 hours. The proline and hydroxyproline in the hydrolysate were separated by using a Dowex-50 (H^+ form) column and radioactivity was counted. The absolute rate of hydroxylation of proline to OH-proline was calculated as described by Ehrhart et al.[13]

Antihypertensive drugs: All antihypertensive drugs were given in drinking water in the following doses:

A. Converting enzyme inhibitor (CEI or SQ 14,225)—45 mg/liter
   +
   Hydrochlorothiazide—500 mg/liter
B. Alpha methyldopa—2.5–5 g/liter
C. Reserpine—0.4 mg/liter
   +
   Hydrochlorothiazide—500 mg/liter
   +
   Apresoline—60 mg/liter
D. Apresoline—80 mg/liter

These drugs were selected because they effectively lowered blood pressure and reversed myocardial hypertrophy in spontaneously hypertensive rats.[14] Ten rats were used in each group.

Results

Effect of hypertension on collagen synthesis: The data on blood pressure and rate of collagen synthesis during evolution of hypertension in spontaneously hypertensive rats and Wistar-Kyoto (control) rats are shown in Figure 1. In the 4 week old hypertensive rats, when blood pressure was not elevated (120 ± 10 versus 112 ± 8 mm Hg), a significant increase in the rate of collagen synthesis was found (52.5 ± 8 versus 17 ± 4 ng collagen/100 mg tissue per 3 hours) (P <0.001). At 8 weeks, a similar increase in the rate of collagen synthesis was observed, except that the blood pressure in the hypertensive rats was significantly elevated (174 ± 6 versus 123 ± 3) (P <0.01). When the hypertensive rats were 10 and 15 weeks old, the rate of collagen synthesis was slightly, but not significantly, elevated (P <0.1) compared with the rate in age-matched control rats, despite persistence of hypertension (191 ± 4 versus 134 ± 3 and 189 ± 5 versus 130 ± 4, respectively) (P <0.001). In rats 24 weeks of age, the rate of collagen synthesis was significantly elevated again (23 versus 11 ng/100 mg per 3 hours) in parallel with sustained hypertension (191 ± 6 versus 125 ± 3 mm Hg).

Effect of antihypertensive therapy: The effect of prevention of hypertension by antihypertensive drugs on heart weight, blood pressure and kidney weight is shown in Figure 2. Hypertension was prevented by all drugs used. Alpha-methyldopa, converting enzyme inhibitor plus hydrochlorothiazide, and a combination of reserpine, apresoline and hydrochlorothiazide prevented the development of hypertrophy in all hypertensive rats. The heart weight/body weight ratios were 2.8 ± 0.02, 2.5 ± 0.03 and 2.8 ± 0.001 mg/g, respectively, compared to 3.3 ± 0.04 mg/g in untreated control rats. Apresoline therapy alone did not prevent the development of hypertrophy, despite giving excellent blood

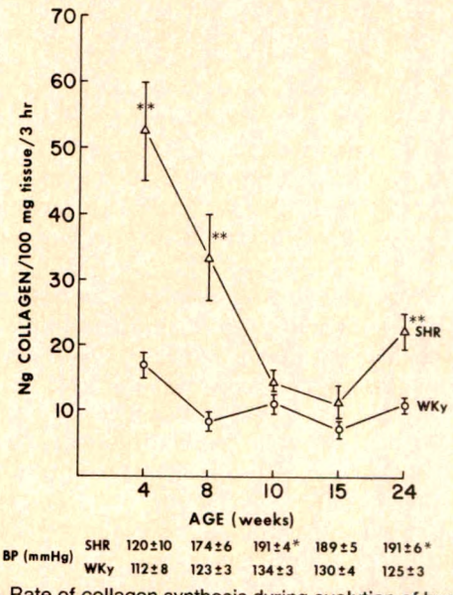

FIGURE 1. Rate of collagen synthesis during evolution of hypertension in spontaneously hypertensive rats (SHR) and Wistar Kyoto (WKy) control rats. BP = blood pressure.

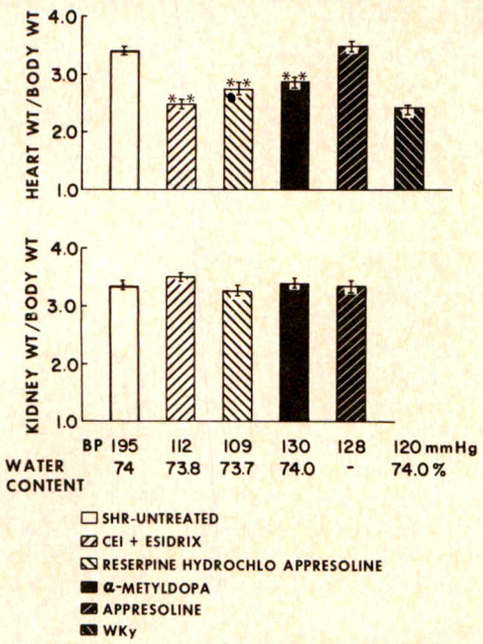

FIGURE 2. Prevention of hypertension in spontaneously hypertensive rats by long-term (6 months) antihypertensive drug therapy. For details of doses, see text. CEI + Esidrix = converting enzyme inhibitor plus hydrochlorothiazide; Hydrochloro = hydrochlorothiazide. Other abbreviations as in Figure 1.

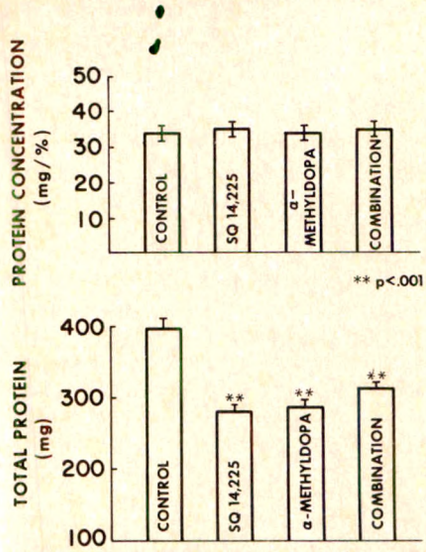

FIGURE 3. Effect of antihypertensive drugs on myocardial protein concentration and total content after prevention of hypertension in spontaneously hypertensive rats. p = probability; SQ 14,225 = converting enzyme inhibitor.

pressure control. The reduction in heart weight was not a nonspecific effect, because the kidney weight/body weight ratio was not altered (Fig. 1). Furthermore, the water content of the myocardium was not different in the treated groups, indicating that the reduction of heart weight was not due to change of water content.

Effect of antihypertensive drug therapy on total myocardial protein is shown in Figure 3. The concentration of protein in the myocardium was not different in the drug-treated hypertensive rats compared with that of untreated control animals (35.4 ± 2.44 (CEI), 34.01 ± 1.42 (alpha methyldopa), and 34.86 ± 2.94 (combination) mg/dl, respectively, in the three treatment groups) compared with 33.76 ± 1.96 mg/dl in untreated hypertensive rats. However, the protein content was significantly reduced with all three drug regimens (280.6 ± 20, 285 ± 16.82, and 330 ± 22 mg, respectively) compared with 394 ± 20 mg in the untreated group ($P < 0.01$).

The collagen concentration and content (mg/ventricle) are shown in Figure 4. As with protein concentration, the myocardial collagen concentration in the treated hypertensive rats was not changed—4.98 ± 0.28 (converting enzyme inhibitor), 4.80 ± 13 (alpha methyldopa) and 5.05 ± 0.49 (combination) mg/g—compared with 4.62 ± 0.26 mg/g in the untreated group (not significant). The content of collagen was significantly reduced because of drug therapy (Fig. 4, lower panel); 3.89 ± 0.25, 3.78 ± 0.15 and 4.1 ± 0.4 mg, respectively, for the three treatment groups, and 5.37 ± 0.36 in untreated control rats ($P < 0.001$ in all cases). The rate of myocardial collagen synthesis of treated and untreated hypertensive rats is shown in Figure 5. The rate of collagen synthesis was significantly reduced with three drug therapy. In untreated hypertensive rats the rate of collagen synthesis was 775.7 ± 145.2 pg/mg protein per 3 hours. In the three treatment groups the rate of collagen synthesis was inhibited to 364.7 ± 77, 479 ± 125, and 387 ± 47.7 pg/mg protein per 3 hours, respectively ($P < 0.001$ for all three groups).

Discussion

Factors altering collagen component of myocardial protein after antihypertensive treatment: This study describes the changes in protein and collagen contents and the rate of synthesis of newly formed collagen during evolution of hypertension and after prevention of development of hypertension by antihypertensive drugs. During the evolution of hypertension, the rate of collagen synthesis was significantly increased in 4 week old spontaneously hypertensive rats (when blood pressure was not yet elevated) and in 24 week old hypertensive rats in parallel with increased heart weight and collagen content.[8] Several questions arise from this observation: (1) Why was the rate of synthesis increased at 4 weeks of age? (2) Why was there a second increase at 24 weeks? (3) Are the triggering stimuli the same in both cases? (4) Is the second increase due to persistent hypertension in spontaneously hypertensive rats? Several investigators[3,15,16] have indicated that in doca-salt hypertensive rats and spontaneously hypertensive rats, blood pressure may have a role in altering the rate of protein synthesis of the cardiovascular system, especially in the aorta and the mesenteric artery. In this study, to investigate the effect of persistent hypertension, spontaneously hypertensive rats were treated with antihypertensive drugs from the prehyp-

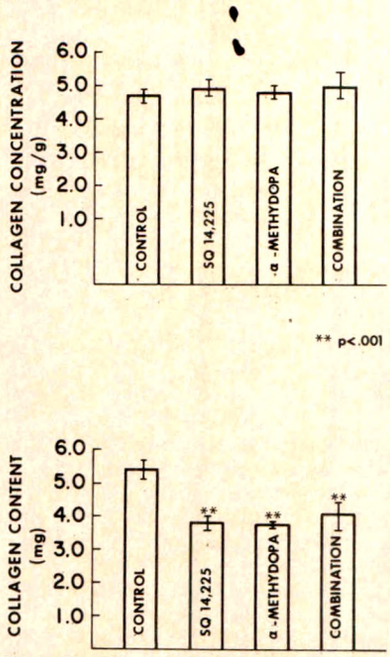

FIGURE 4. Effect of antihypertensive drugs on myocardial collagen concentration (mg/g ventricle) and content (mg/ventricle) after prevention of hypertension in spontaneously hypertensive rats. SQ 14,225 = converting enzyme inhibitor.

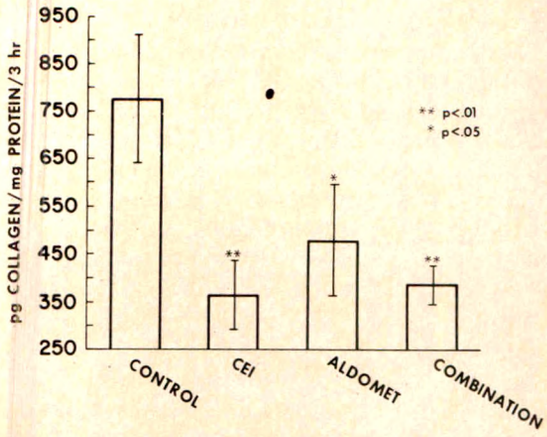

FIGURE 5. Effect of long-term antihypertensive therapy with three treatment regimens on rate of myocardial collagen synthesis after prevention of hypertension in spontaneously hypertensive rats. CEI = converting enzyme inhibitor; p = probability.

ertensive state at 3 weeks to 24 weeks of age. All three drug regimens not only prevented the development of hypertension, but also reduced the rate of collagen synthesis, and actually lowered the collagen content of the heart. The reduction in collagen is somewhat different from that which we have reported. In our previous study[17] we showed that short-term (3 to 6 weeks) therapy with alpha methyldopa administered to 8 week old spontaneously hypertensive rats reversed myocardial hypertrophy. The concentration of collagen in the heart in these rats was increased from 4.0 ± 0.13 to 4.89 ± 0.26 mg/g ($P < 0.01$), whereas the content remained the same because of the smaller size of the heart (3.75 mg versus 3.80 mg). This observation indicated that duration of drug therapy or the age of the hypertensive rat could be an important factor in altering the collagen component of myocardial protein.

Role of hypertension: The response of the vascular system to hypertension appears to be similar to that of the heart. Hollander et al.[6] reported that thickening of the aorta in the spontaneously hypertensive rat was associated with an increased content of collagen and protein. These changes were detectable as early as 2 weeks after birth. The increased content of collagen could be prevented by antihypertensive drug therapy.[4,6] An increase in collagen content may alter cardiac performance. Averill et al.[18] reported that in chronic renal hypertensive rats, ventricular performance was significantly reduced, and the ventricles of these rats had higher collagen content. However, whether cardiac performance was reduced in the spontaneously hypertensive rat was not established. Hollander et al.[6] reported that antihypertensive drug treatment in the hypertensive rat can arrest the progression of hypertensive cardiovascular disease and cause significant regression. These observations are consistent with the clinical findings in hypertensive men reported by Freis et al.[7]

In young spontaneously hypertensive rats, as hypertension is developing, a negative correlation between rate of collagen synthesis and blood pressure was noted (Fig. 1). This suggested that the increase of rate of collagen synthesis at 4 and 8 weeks was independent of the rise in blood pressure. In contrast, in older spontaneously hypertensive rats, the rate of collagen synthesis was increased in parallel to increased blood pressure. This second increase could be due to the long-standing hypertension. That hypothesis is supported by the successful prevention of the second rise in collagen synthesis by long-term antihypertensive therapy (Fig. 5). Thus, an intriguing dissociation in collagen synthesis was found between younger and older hypertensive rats; only the latter was related to hypertension.

Factors altering myocardial protein synthesis in hypertensive heart disease: The exact stimulus for the alteration of myocardial protein synthesis in spontaneously hypertensive rats is not clear. In the very young rats, in which blood pressure is normal or nearly normal, the stimulus may be a humoral factor like growth hormone, or a hemodynamic abnormality such as hyperkinetic circulation. In the older rats, however, long-standing hypertension appeared to play the more important role. In the latter case, it is likely that stimulation of protein synthesis in hypertensive cardiovascular disease is largely related to structural damage to the heart and blood vessels caused by long-standing increased pressure. Other authors[19] have reported reduction of collagen content in vessels of hypertensive rats by antihypertensive therapy; our study appears to be the first one documenting the reversal of the content

as well as the rate of collagen synthesis in the myocardium of spontaneously hypertensive rats.

Implications: The quantity of collagen in the myocardium is believed to be an important factor in hypertension because accumulation of collagen or fibrous tissue might reduce cardiac performance. Furthermore, duration of antihypertensive treatment seems to be important in the reversal of collagen. Further studies are necessary to determine whether or not age at start of treatment and type of collagen are also important factors in the reversal of collagen accumulation.

Acknowledgment

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Is Arterial Pressure the Sole Factor Responsible for Hypertensive Cardiac Hypertrophy?

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Increased arterial pressure is obviously the major stimulus to cardiac hypertrophy in hypertension. However, different studies suggest that in addition to the pressure load, other factors could play participating roles in determining the degree of ventricular hypertrophy in response to the hypertensive disease as well as the degree of its reversal after control of arterial pressure. These other mechanisms include genetic factors and concomitant processes such as aging and the presence of cardiomyopathy or other disease. Two neurohumoral influences, namely, the adrenergic and the renin-angiotensin systems, may also participate, and the early evidence supporting these possible contributing factors is cited. Further studies are needed to determine the relative importance of each of these factors in different types of hypertension and in their response to different modes of antihypertensive therapy.

Two major variables account for the tension developed by the myocardium: the intravascular pressure and the diameter of the heart. In progressive systemic hypertension these two variables change. Thus, as hypertensive vascular disease progresses so does the total peripheral resistance and thus the afterload imposed on the left ventricle.[1,2] One of the adaptive responses of the left ventricle to this increasing afterload is hypertrophy, which may be of different types with different effects on the diameter of the left ventricle.[3,4] The second response is the mobilization of different mechanisms (for example, Frank-Starling mechanism, homeometric regulation) in order to overcome the increased resistance to ejection and allow adequate flow to the periphery. Thus, both components of the tension developed by the left ventricle (pressure and diameter) increase in hypertension and these increases account for the progressively increasing myocardial oxygen consumption in hypertensive vascular disease.

Development of Ventricular Hypertrophy: The Meerson Hypothesis

In response to its increased work the left ventricle increases its mass. Linzbach[4] suggested that the ventricle adapts by means of this hypertrophic response according to the work load imposed on the myocardium. Under the conditions of a volume overload, the ventricle adapts with a process of eccentric hypertrophy, but when the overload of the ventricle is induced by pressure, the left ventricle adapts, at least initially, with concentric hypertrophy. The hypertrophic process is therefore not uniform but appears to be adapted to suit the nature of the work load imposed on the muscle itself.[5]

Ten years ago, Meerson[6] described a pathophysiologic sequence for the development of left ventricular hypertrophy. In this concept, the immediate response to a hypertrophy-inducing stimulus imposed on a normally functioning heart is one of a physiologic hyperfunction associated with an increase in myocardial protein synthesis. Thus, initially

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the left ventricle increases its force of contraction to overcome the imposed pressure or volume work; simultaneously, the ventricle also responds chemically by increasing ribonucleic acid (RNA) synthesis to enhance the amount of protein subunits necessary for myocardial contraction.[7] As the ventricular work load persists, the myocardium must continue to adapt by means of this hypertrophic process or else it will fail to respond to the sustained demands made upon it.

Thus, the heart responds in two fashions to the increased work demand: physiologically and biochemically.[8] It is not clear how the two responses are linked or how the pressure load is transformed into a biochemical response, but both mechanisms are obviously needed. The biochemical changes are necessary for the long-term continuing response; however, the physiologic responses must also occur to overcome the imposed demands of work load. Thus, even before left ventricular mass is increased, myocardial function is enhanced in order to overcome its increased pressure work load. Nevertheless, as the biochemical response develops with the pressure demands, the hypertrophy itself is thought to provide for a period of stable hyperfunction that enables the myocardium to perform normally in the face of the increased demands imposed upon it. According to Meerson,[6] the myocardium will respond to its maximum in this process of anatomic adaptation; however, eventually, if the progressively increasing afterload persists, ventricular failure will supervene. In general, this appears to be the sequence of events in hypertensive heart disease, but a closer look at various types of experimental hypertension raises questions regarding other mechanistic explanations.

Prerequisites for the Testing of Hypotheses in Hypertension

To test Meerson's hypothesis, it is necessary to induce a state of systemic hypertension that should preferably develop naturally and depend on increased vascular resistance, mainly at the level of the arterioles. In this fashion, then, one could induce a counterpart in the laboratory for the slowly progressive ventricular afterload in essential hypertensive vascular disease. Several experimental models have been developed, including aortic banding and renal arterial clipping (Goldblatt hypertension). However, these processes are so rapidly induced (relatively) that the model does not simulate chronic, slowly progressive, naturally developing systemic hypertension or may be associated with certain pressor mechanisms that are not analogous to essential hypertension in human beings.[2,8,9] For example, in Goldblatt hypertension, the renopressor system may be involved or the loss of renal excreting function may induce disturbances in sodium (and water) balance. In other models, the addition of excessive exogenous sodium or steroids may also be involved. With aortic banding, the Windkessel function of the large arteries is impaired. In an effort to overcome these experimental drawbacks, certain investigators have used slow and long-term infusion of pressor substances that serve to stimulate or promote arteriolar constriction. However, even this intervention may be associated with additional ventricular changes produced by the infused agent itself (for example, myocardial fibrosis) that are over and above those of the induced hypertrophy.[10,11] Thus, an experimentally developed laboratory model for essential hypertension is not readily available; it entails constraints in rate of development, site of the increased vascular resistance and differences in balance of pathophysiologic mechanisms, all of which may influence ventricular response. All models can reveal particular facets of great interest but caution is needed in translating conclusions to the large problem of essential hypertension.

Recently, some small animal models have been developed genetically to produce a naturally developing, slowly progressive ventricular hypertrophy resulting from a progressive increase in total peripheral resistance (arteriolar constriction). The question thus is whether this sequence of events is analogous to the events that have been found in patients with essential hypertension.

The Heart in Essential Hypertension

By studying a sufficient number of patients with essential hypertension, it became possible to classify a progression of systemic hemodynamic and ventricular function associated with the development of essential hypertensive heart disease.[1,2,8] The patients studied (1) had not received antihypertensive medication for a sufficiently long time to preclude the remaining effects of drugs; (2) were studied under the same condition of overnight fasting in the same laboratory circumstances; and (3) were of the same sex and as close to the same age as possible. Under these circumstances, laboratories [12,13] in various countries reported similar hemodynamic findings in the early borderline (labile) state of essential hypertension. Patients with stable essential hypertension have been categorized according to roentgenographic, electrophysiologic or echocardiographic evidence of cardiac involvement with hypertension. Thus, patients with minimal, but early left ventricular hypertrophy, as indicated by the electrocardiographic criteria of left atrial abnormality,[14] had increased left ventricular mass and wall thickness on echocardiography,[15] although there was no X-ray or electrocardiographic evidence of left ventricular hypertrophy at this stage. Patients with obvious chest X-ray, electrocardiographic and echocardiographic evidence of left ventricular hypertrophy[1,15] had a further increase in left ventricular mass and wall thickness. Functionally, these groups of patients represented a continuum in severity of essential hypertensive vascular disease that was reflected in progressive anatomic evidence of ventricular hypertrophy and impaired myocardial function in response to progressively increasing arterial pressure and total peripheral resistance.[1,2,15]

If these group averages are interpreted as stages in the evolution of hypertensive disease, one might make a case that this progression is in accord with Meerson's concept.[6] Patients with essential hypertension often show an early phase of increased performance of the left

ventricle (for example, in borderline and mild essential hypertension); with further myocardial adaptation to the increasing total peripheral resistance (that is, afterload) left ventricular mass progressively increases during a period of stable hyperfunction. However, this period of stable function in hypertrophy is limited and, with severe left ventricular hypertrophy, there is some decrease in the resting performance of the heart until ventricular failure eventually supervenes.

The Heart in the Spontaneously Hypertensive Rat

In contemporaneously designed studies using the genetic strain of spontaneously hypertensive rats (Aoki and Okamoto), similar findings were demonstrated in both the open chest, anesthetized preparation[16,17] and in conscious and unrestrained rats.[18,19] These findings demonstrated that early in the development of hypertension there also seems to be a period of stable hyperfunction.[16,18,20] However, this stage of adaptive hypertrophy is limited and, eventually, myocardial performance becomes impaired with respect to normotensive age- and sex-matched control animals.[21–23]

Thus, there exist both laboratory data and clinical evidence to support the concept promoted by Meerson that the process of hypertrophy follows the physiologic needs of the myocardium. Initially, there is a period of hyperfunction that in time stabilizes as hypertrophy keeps pace with the functional demands imposed on the myocardium. However, with time and progression of the disease, these functional demands no longer can be met by the myocardium. Initially, perfusion may be maintained, thereby satisfying resting tissue needs, but even in this stage myocardial contractility may be impaired. Ultimately, this impaired ventricular contractility is associated with reduced systemic tissue perfusion, and cardiac failure supervenes.

Shortcomings of the Findings

Nevertheless, there are several findings, that point to a more complex situation than a direct relation between pressure and hypertrophy. Thus, early in the development of hypertension in the spontaneously hypertensive rat, the degree of left ventricular hypertrophy may be out of proportion to the elevation of arterial pressure.[21,22,24,25] Indeed, some investigators[24–27] suggested that a prehypertensive state, associated with ventricular hypertrophy, seemed to exist in the spontaneously hypertensive rat. However, other laboratories[20,21] indicated that even in these so-called prehypertensive stages arterial pressure itself was significantly higher than in normotensive control strains (American Wistar and the Wistar-Kyoto rats). Whether the pressure was higher than in the normotensive strains or whether the pressure was the same, ventricular hypertrophy seems to have existed at the time of birth, not only in the left ventricle but also in the right.[21,25]

Thus, two critical questions remain to be answered: (1) Do hemodynamic factors alone provide sufficient evidence to explain the progressive increase in ventricular mass in hypertension; and (2) if other factors (in addition to afterload) do participate in the pathogenesis and maintenance of left ventricular hypertrophy, what are they? Related but subordinate questions might include: (a) Why does right ventricular hypertrophy occur; (b) is the muscular hypertrophy a generalized cardiovascular phenomenon in systemic hypertension involving arterioles, veins and myocardium; (c) can myocardial hypertrophy be prevented by treatment and does it regress with treatment once it has developed; and (d), if the latter is demonstrable, can pharmacologic interventions teach us something about the mechanisms involved in the development of hypertrophy?

TABLE I

Cardiac Hypertrophy in Hypertension: Factors Other Than Increased Afterload

1. Hemodynamic factors other than resistance to ventricular ejection
   a. Increased heart rate
   b. Alterations in cardiac output
2. Neurohumoral factors
   a. Renin-angiotensin system
   b. Adrenergic stimulation and catecholamines
3. Concomitant processes
   a. Physiologic: aging
   b. Pathologic: other myocardiopathy (including atherosclerotic ischemic heart disease, diabetes mellitus and other conditions)
4. Genetic predisposition
5. Altered myocardial composition
   a. Possible effects of increased collagen deposition
   b. Altered myocardial metabolism

Not to be forgotten in these considerations is a fundamental question for clinicians: Is the knowledge derived from experimental hypertensions at all germane to clinical essential hypertension? The many discrepancies between various experimental models and the human situation have already been mentioned. Recent studies seem to indicate that even spontaneous hypertension in animals might not be a totally adequate model. The spontaneously hypertensive rat might have an additional myocardial problem not necessarily related to its hypertension.[25] Perhaps, it is only from an integration of information from various sources that an outline of the spectrum of cardiac response to hypertension can be developed.

Other Possible Causes of Hypertrophy

What does account for the progressively increasing mass in addition to the mechanical effect of the pressure load imposed on the myocardium? Studies even in more severely hypertensive spontaneously hypertensive rats show that left ventricular mass progressively increases and that this increase continues even after arterial pressure has achieved a plateau.[16,20,21] Several explanations may be offered for the frequent discrepancies between pressure load and degree of left ventricular hypertrophy (Table I). Badeer[28] has emphasized the role of heart rate in the development of cardiac hypertrophy. Associated diseases can obviously alter the hypertrophic process, but the role of certain physiologic processes such as aging are often overlooked. The aging myocardium progressively increases in mass, and this

in itself may explain the increased mass over and above the pressure demand.[29] Moreover, as left ventricular mass increases with time, it is associated with an increased collagen deposition in the myocardium.[30,31] The full hemodynamic effect of that alteration in myocardial composition still needs to be determined. Because of their frequent participation in the initiation and evolution of hypertension, disturbances in neurohumoral factors can be of special importance in modulating cardiac responses in hypertensive diseases. This includes not only the development of hypertrophy but also its response to antihypertensive treatment.[30]

Regression of Hypertrophy

Disparate response to antihypertensive therapy: Several reports have indicated that reduced left ventricular pressure work load and total peripheral resistance may not necessarily be associated with reduction of left ventricular mass. Early studies by Hall et al.[32] had demonstrated reversal of cardiac hypertrophy after surgical cure of experimental hypertension. Freis et al.[33] showed that treatment of spontaneously hypertensive rats with the same combination of drugs (reserpine, hydralazine, hydrochlorothiazide) as that used in the Veterans Administration Cooperative Study, prevented an increase in left ventricular mass as long as arterial pressure remained controlled. Sen et al.[24,30,34] reported both prevention and reversal of hypertrophy with other antihypertensive agents (methyldopa and captopril); but they also noted that hypertrophy could not be prevented or reversed by vasodilator drugs although the latter provided equally good blood pressure control.[24,35] Although the pressure work of the left ventricle was reduced pharmacologically to the same extent with vasodilating agents as with methyldopa, left ventricular mass did not change similarly.

The renin-angiotensin hypothesis: These results suggested that one or more factors in addition to pressure reduction could play a significant role in modulating hypertrophic responses to altered pressure loads. Of particular importance, apart from possible differences in hemodynamic effects, are differences in neurohumoral effects of various antihypertensive drugs. Thus plasma renin activity was decreased after methyldopa[24,30] but elevated after minoxidil and hydralazine.[35] This circumstantial evidence was given support by the observation that angiotension II led to increased protein synthesis in myocardial and smooth muscle cells.[36] However, the occurrence of left ventricular hypertrophy in primary aldosteronism[37] and other low renin hypertensions[38] as well as studies with angiotensin antagonists[39] raises some doubts regarding the importance of the renin system in hypertensive cardiac hypertrophy,[40] and the question is still a subject of active debate.

Role of adrenergic factors in hypertrophy: An alternative to the renin-angiotensin hypothesis is the possible role of adrenergic factors acting either directly or through a faster heart rate. Thus, it is possible that methyldopa, in addition to reducing arterial pressure and inhibiting the release of renin from the kidney, also reduces cardiac adrenergic drive,[41] in contrast with myocardial stimulation reflexly induced by vasodilators. Exogenous catecholamines will provoke a hypertrophic response,[42] whereas administration of guanethidine will prevent myocardial hypertrophy in rats in response to exercise.[43] However, prolonged beta adrenergic blocking treatment of spontaneously hypertensive rats, even from preconception to postnatal development, has not been associated with reduction in left ventricular mass despite reduction of adrenergic stimulation of the myocardium.[44] The precise role of adrenergic influences in hypertensive cardiac hypertrophy remains to be determined; myocardial catecholamine concentration in spontaneously hypertensive rats is not reduced in contrast with its usual reduction in other types of "pressure hypertrophy."[45]

Clinical implications: There is little doubt that, despite the possible modulating role of various neurohumoral factors, the major mechanism responsible for cardiac hypertrophy in hypertension is the increased pressure load. However, the many discrepancies among patients between pressure level and cardiac size[46] and the differential response to antihypertensive therapy[24] suggest that other factors—which may differ in different cases—must be taken into account. Whether these include the renopressor, adrenergic or other factors remains unknown at this time. Genetic and species differences could undoubtedly influence the impact of hypertension on the heart, as could socioeconomic conditions suggested by clinical observations.[47]

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Cardiac Hypertrophy in Early Hypertension

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Studies of cardiac hypertrophy in spontaneously hypertensive rats have indicated that left ventricular hypertrophy occurred even in the prehypertensive stage. These findings suggested that other factors besides blood pressure levels, and including possibly a genetic predisposition to myocardial hypertrophy, could play a role in structural cardiovascular alterations in spontaneously hypertensive rats. More recent studies have confirmed these anatomic results; left ventricular hypertrophy was vectorcardiographically detected even in the prehypertensive stage in both young stroke-prone rats and stroke-resistant spontaneously hypertensive rats. Further, a close relation was found between degree of left ventricular hypertrophy and vascular hypertrophy or hyperplasia; this suggests that early detection of left ventricular hypertrophy may be a useful indicator of the incipient stage of structural vascular changes in genetic hypertension.

In spontaneously hypertensive rats,[1] which are widely used as animal models for essential hypertension,[2,3] not only hypertension but also its cardiovascular complications develop. Cardiac hypertrophy, nephrosclerosis and cerebrovascular lesions (cerebral hemorrhage and infarction) are the three major complications of spontaneous hypertension in rats as they are of essential hypertension in man. These complications, however, are not only the result of the increased arterial pressure, which plays a dominant but not the only role in the disorder. Our earlier studies[4–7] pointed out the importance of genetic factors in the development of at least two complications, ventricular hypertrophy and cerebrovascular lesions.

In 1974, stroke-prone spontaneously hypertensive rats were selectively bred from our strain of spontaneously hypertensive rats.[5] In more than 90 percent of stroke-prone spontaneously hypertensive rat colonies strokes develop spontaneously, which indicates the importance of genetic selection in this hypertensive complication. Similar conclusions were reached regarding cardiac hypertrophy, which is the most common complication of hypertension. Various grades of hypertrophy can be found among spontaneously hypertensive rats at different stages of their development.[6–9] Although this hypertrophy is often considered only a secondary effect of the increased pressure load, findings in very young spontaneously hypertensive rats suggested again a more complex picture. Significant ventricular hypertrophy was reported in these rats in the absence of significant differences in arterial pressure.[7,8,10,11] One could relate this early hypertrophy, by analogy with cerebral lesions, to a possible genetic influence, but other factors could also play a significant role.

In the present review, we have examined again the evidence for early cardiac hypertrophy in spontaneously hypertensive rats and its correlation with vascular changes. Early structural alterations of the heart

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in spontaneous hypertension are of particular importance not only because of their pathophysiologic aspects, but also because of their potential clinical implications. Recognition of ventricular hypertrophy in children or adolescents with borderline elevation of arterial pressure would, if documented, help the physician to make a more precise assessment of their status and possible need for therapy.

Early Cardiac Hypertrophy in Young Spontaneously Hypertensive Rats

Factors accounting for discrepancy between cardiac hypertrophy and level of blood pressure: The heart weight of the spontaneously hypertensive rat was significantly greater even at the age of 30 days than in age- and body weight-matched Wistar-Kyoto control rats[7] (Fig. 1), although no significant difference in blood pressure could be documented at this very young age. This early cardiac hypertrophy in prehypertensive rats was also reported independently by Sen et al.[8] Not only was the heart weight clearly increased in these young spontaneously hypertensive rats, but there were also found biochemical alterations, such as increased myocardial incorporation of labeled amino acids[10] and increased cardiac enzyme activity (monoamine oxidase).[7] The discrepancy between the insignificant increase in arterial pressure and the early ventricular hypertrophy pointed to the possible intervention of factors other than the increased pressure. One possibility was that ventricular hypertrophy could be dependent in these animals on genetic factor(s) that were either related or merely linked to their genetic predisposition to hypertension. Cutilletta et al.[11] advanced the hypothesis of an independent myocardiopathy for which, however, there was no firm evidence either pathologically[12] or hemodynamically.[9] Apart from these two possibilities, other possibilities that are not necessarily contradictory could also account for the discrepancy between cardiac hypertrophy and level of blood pressure.[13,14]

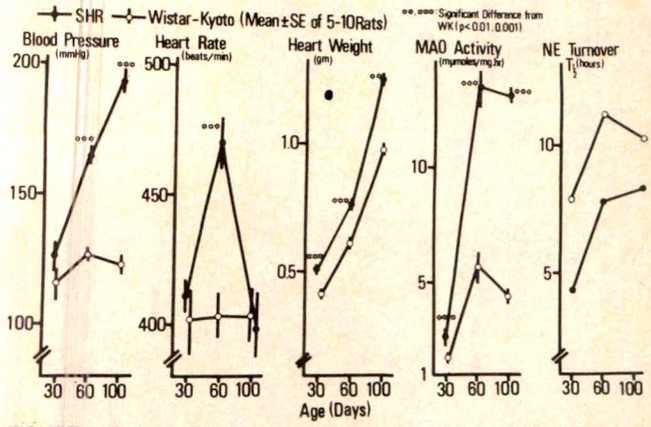

FIGURE 1. Early cardiac alteration in young spontaneously hypertensive rats (SHR) compared with findings in normal Wistar-Kyoto (WK) rats. MAO = monamine oxidase; NE = norepinephrine; p = probability; SE = standard error; $T^1/_2$ = half-life.

Role of increased adrenergic activity: Of these possible mechanisms, increased adrenergic activity may be of particular importance in the early development of myocardial changes in the young spontaneously hypertensive rat. This hypothesis is supported by the prominence of neurogenic factors in the early stages of spontaneous hypertension[3,13]; moreover, we[7] have documented an accelerated cardiac norepinephrine turnover at 30 and 60 days after birth. It is conceivable, therefore, that the early development of left ventricular hypertrophy in this model could be related to or influenced by increased sympathetic nervous activity. In fact, the increased cardioadrenergic drive might play an equally if not more important role than the small and often insignificant differences in blood pressure at this age. Although Cutilletta et al.[11] reported persistance of left ventricular hypertrophy even after peripheral sympathectomy in the spontaneously hypertensive rat, their results do not necessarily contradict this hypoth-

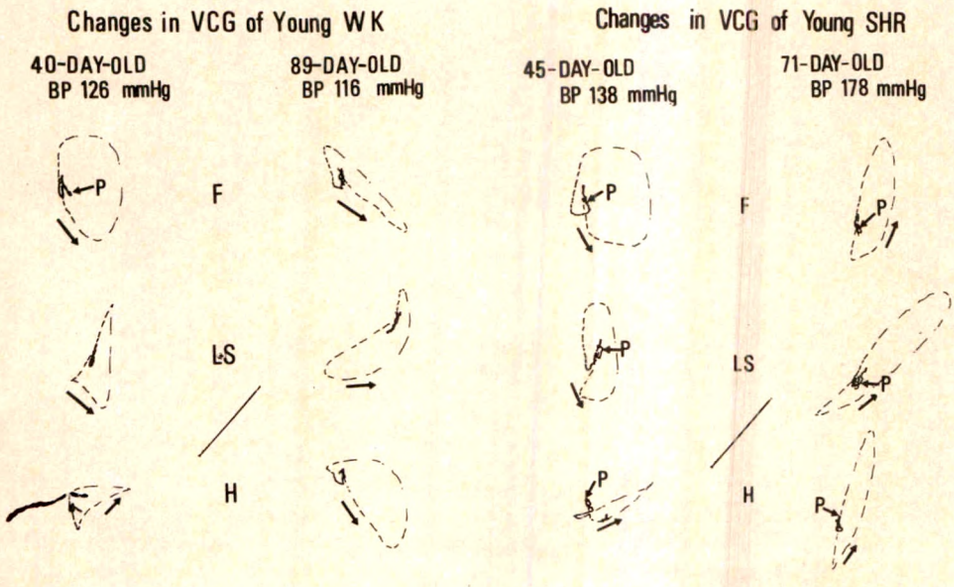

FIGURE 2. Left, changes in vector cardiogram (VCG) of a young Wistar-Kyoto (WK) rat compared with findings in a young spontaneously hypertensive rat (SHR) (**right**). BP = blood pressure; H = horizontal; LS = left sagittal; p = P wave.

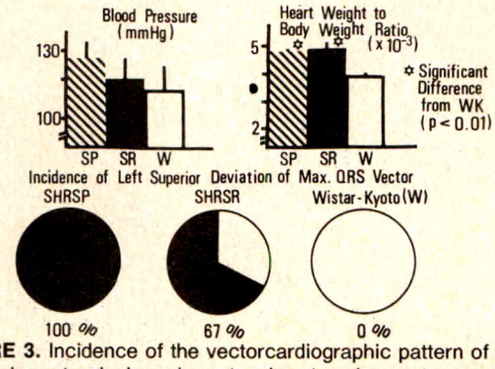

FIGURE 3. Incidence of the vectorcardiographic pattern of left ventricular hypertrophy in prehypertensive stage in spontaneously hypertensive rats (SHR) (both stroke-resistant [SR] and stroke-prone [SP] compared with that in normal Wistar-Kyoto [WK] rats. Max. = maximal; p = probability.

esis. Adrenomedullary catecholamines are compensatorily activated after sympathectomy and their influence could replace the drive lost from attempts at denervation.

Vectorcardiography to detect early left ventricular hypertrophy: In order to detect the earliest signs of cardiac hypertrophy more easily than can be done by observation of morphologic and biochemical changes, a vectorcardiographic method was developed for small animals.[6] Reproducible vectorcardiograms could be obtained in young spontaneously hypertensive rats by using four large electrodes around the thorax and two small electrodes on the head and tail.[15] This technique was applied to young stroke-prone and stroke-resistant spontaneously hypertensive rats of various age groups, and results in these two strains were compared with findings in closely matched Wistar-Kyoto control rats. In normotensive Wistar-Kyoto rats the vectorcardiogram showed a left downward orientation of the maximal QRS vector at all ages. The basic normotensive pattern of the vectorcardiogram was well maintained even in rats older than 1 year of age. In contrast, in adult stroke-prone spontaneously hypertensive rats there was a consistent typical left upward deviation of the maximal QRS vector (Fig. 2, right). Old spontaneously hypertensive rats also showed these deviations of the QRS loop with prolonged QRS duration and characteristic ST-T changes.[16,17] This deviation from the norm appeared to be the common sign of left ventricular hypertrophy, not only in spontaneously hypertensive rats but also in rats with renal hypertension.

Because these vectorcardiographic recordings in rats were confirmed to be reproducible and reliable, detailed vectorcardiographic changes were studied in very young spontaneously hypertensive rats while their blood pressure course was carefully monitored.[15] The typical left upward deviation of the maximal QRS vector in hypertensive spontaneously hypertensive rats was already noted in prehypertensive stroke-prone rats at the age of 30 to 40 days, when the systolic blood pressure was still only 130 to 140 mm Hg. These vectorcardiographic patterns of left ventricular hypertrophy suggest that hypertrophy is developing quite early in life, especially in the stroke-prone spontaneously hypertensive rat with a genetic disposition to severe hypertension. The incidence of these patterns among 30 to 40 day old rats was 100, 67, and 0 percent, respectively, in groups of stroke-prone spontaneously hypertensive rats, stroke-resistant spontaneously hypertensive rats and Wistar-Kyoto control rats (Fig. 3). In our experience, the presence of left ventricular hypertrophy in the prehypertensive stage has been a constant finding in stroke-prone rats. Of particular importance was the contrast among these three groups between the variation in incidence of left ventricular hypertrophy and the absence at that age of differences in blood pressure. The cardiac weight at that time was significantly greater both in stroke-prone and in stroke-resistant spontaneously hypertensive rats than in Wistar-Kyoto rats.

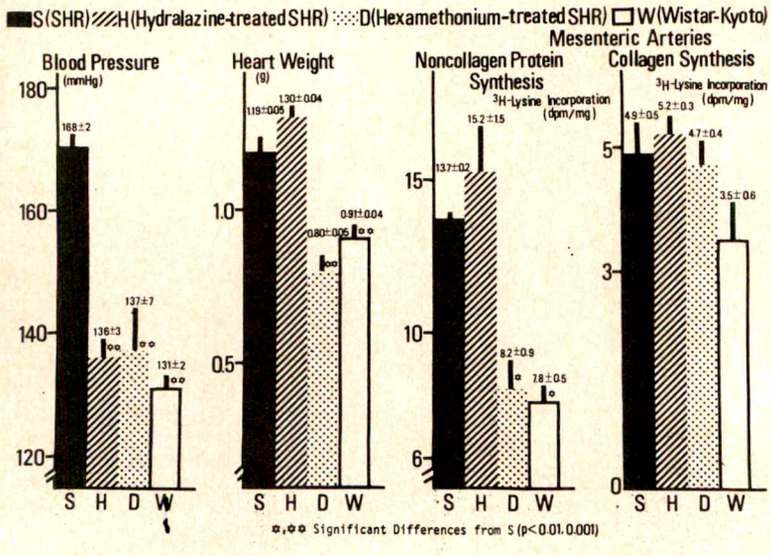

FIGURE 4. Effect of antihypertensive therapy on cardiovascular hypertrophy in spontaneously hypertensive rats (SHR).

TABLE 1

Blood Pressure, Heart Weight and Incorporation of ^{3}H-Lysine into Mesenteric Arteries of Treated and Untreated Spontaneously Hypertensive Rats (SHR)* and Untreated Wistar-Kyoto Rats (WK) (mean ± standard error)

Experimental Groups (no. of rats)	Blood Pressure (mm Hg)	Heart Weight (g)	Mesenteric Arteries (dpm/100 g wet weight)
I. Untreated SHR (no. = 10)	168 ± 2	1.19 ± 0.05	1374 ± 23
II. Hydralazine-treated SHR (no. = 10)	136 ± 3†	1.30 ± 0.04	1517 ± 152
III. Hexamethonium-treated SHR (no. = 9)	136 ± 7†	0.80 ± 0.05†	824 ± 95†
IV. Splanchnicotomized SHR (no. = 10)	136 ± 3†	1.05 ± 0.05	790 ± 29†
V. Untreated WK, (no. = 8)	131 ± 2	0.91 ± 0.04†	777 ± 48†

* From Yamori et al.[20]
† Probability [P] <0.001 (compared with value in Group I).

In summary, the early incidence of cardiac hypertrophy seems well established in spontaneously hypertensive rats of different strains (stroke-prone and stroke-resistant). This structural alteration, which is evident in the absence of significant elevations in blood pressure, may be related to or merely linked with a genetic predisposition to hypertension or it could be evoked or accentuated by hypertensive mechanisms already active before the development of overt hypertension.

Relation Between Cardiac and Vascular Hypertrophy

Accelerated vascular and cardiac protein synthesis: The importance of structural vascular changes in the pathogenesis of hypertension was stressed in both clinical and experimental forms of the disease.[18] We have repeatedly shown that neurogenically induced vasoconstriction in the incipient stage of hypertension was rapidly followed by accelerated synthesis of vascular proteins, including both collagenous and noncollagenous types of protein.[3,7,13,19,20] This increased synthesis results in medial hypertrophy and thickening of the vessel wall. Noncollagen protein synthesis in peripheral vessels was particularly enhanced in early hypertension and this was demonstrable even in the "prehypertensive stage."[7,21] This early acceleration of vascular protein synthesis appears analogous to the early development of cardiac hypertrophy. It is possible that both are related to or dependent on similar mechanisms. The possible temporal relation between cardiac and vascular hypertrophy was further analyzed in vitro; the incorporation of labeled leucine was clearly accelerated in the mesenteric arteries and the aorta of spontaneously hypertensive rats and tended to be increased in the heart even at 4 weeks.[22] These results were consistent with the reported increased incorporation of labeled lysine into cardiac myosin in spontaneously hypertensive rats as compared with age-matched Wistar-Kyoto rats.[10] Thus, protein synthesis appeared to be accelerated concomitantly in both the heart and the peripheral vessels of young spontaneously hypertensive rats.

Effect of antihypertensive treatment: This coincidence between changes in heart weight and rate of vascular protein synthesis was further observed in Wistar-Kyoto rats and in spontaneously hypertensive rats treated with various antihypertensive agents.[20] Details of this study have been published previously[20]; one example of these experiments is reported in Figure 4. Both a vasodilator (hydralazine, 80 mg/liter in drinking water) and a ganglion-blocking agent (hexamethonium, 50 mg/kg, given subcutaneously two times daily) clearly reduced blood pressure in spontaneously hypertensive rats to normotensive levels. However, the

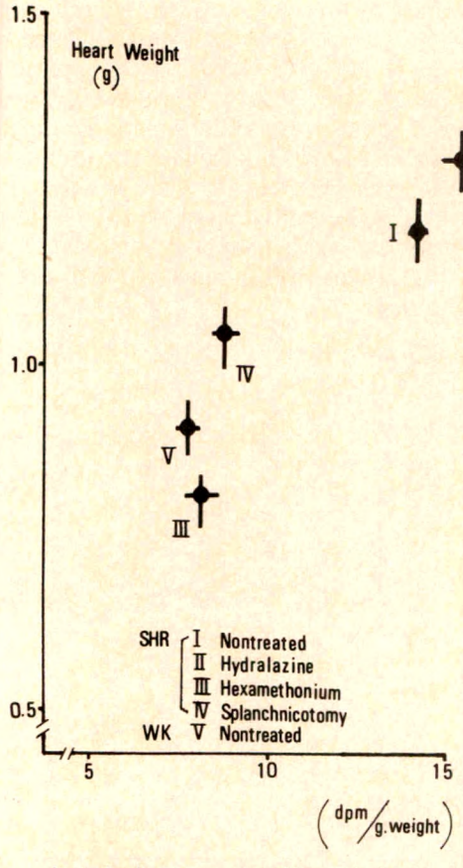

FIGURE 5. Relation between heart weight and vascular protein synthesis in treated and untreated spontaneously hypertensive rats (SHR) and in normal untreated Wistar-Kyoto (WK) rats.

vasodilator was not effective either for reducing heart weight or for attenuating noncollagen protein synthesis in mesenteric arteries. In contrast, pharmacologic denervation effectively reduced both heart weight and vascular noncollagen protein synthesis.[20] Eventually, similar results were obtained in mesenteric vessels after surgical sympathectomy (that is, splanchnicotomy with complete denervation of mesenteric arteries).[20] The increased incorporation of lysine into noncollagenous protein of mesenteric vessels in spontaneously hypertensive rats was consistently abolished by treatment with hexamethonium or by splanchnicotomy, but was not affected by treatment with hydralazine (Table I).

Whether denervation was obtained pharmacologically or by surgery, a positive correlation was consistently found between heart weight and vascular protein synthesis in mesenteric arteries (Fig. 5). Many explanations could be advanced for this correlation; both changes could reflect the influence of the same factors, be they neurogenic or humoral. Another possibility is that the structural change in vessel walls and their thickening contributes to increased peripheral resistance and thus indirectly to cardiac load. In any event, an important practical result for studies of pathologic mechanisms or of drug effects was that left ventricular hypertrophy appeared to be a good indicator of the hypertrophy or hyperplasia of peripheral arterial walls.

Coronary arterial changes: Histologic studies further demonstrated that thickening of small coronary arteries due to medial hypertrophy or hyperplasia and occlusive arterial changes with thrombosis were often observed in the hypertrophied heart of adult spontaneously hypertensive rats. In the advanced stage, intraluminal proliferative changes are so marked that the arterial lumen is almost occluded, and such arterial hyperplasia coexists with myocardial hypertrophy. The ratio of the lumen to the transectional area of small coronary arteries (diameter of less than 100 and between 100 and 150 μ) was determined histometrically in laboratories using a quantitative picture analysis (MOP-AM, 3, Kontrone). The investigation involved stroke-prone and stroke-resistant spontaneously hypertensive and Wistar-Kyoto rats from 1 to 12 months of age with 5 to 10 rats in each group. The normal ratio was clearly and significantly reduced even in young 1 month old spontaneously hypertensive rats as compared with their age-matched Wistar-Kyoto counterpart. Furthermore, there seemed to be an inverse correlation between heart weight and the lumen to transectional area ratios of coronary arteries in spontaneously hypertensive and Wistar-Kyoto rats from 1 to 6 months of age (Fig. 6). Again, cardiac weight hypertrophy seemed to be a good indicator of vascular hypertrophy or hyperplasia, that is, for those structural vascular changes that are important in the further development and maintenance of hypertension.

Clinical Echocardiographic Studies

These experimental observations in spontaneously hypertensive rats suggested that cardiac hypertrophy might develop early in life in persons with borderline elevations in arterial pressure or some predisposition to hypertension. If documented, this early incidence of cardiac hypertrophy could prove of major significance in our understanding of the disease and approach to its control. An extensive survey of schoolchildren in Japan was therefore undertaken involving more than 350 children aged 6 to 15 years (Shimane Heart Study).[23,24] Details of the methods have been published previously; of special relevance to the subject of cardiac hypertrophy were the results obtained with echocardiography in the 22 children with borderline hypertension. The extensive analysis of echocardiography in 369 normotensive children allowed the development of normal values for different age groups. Viewed against this

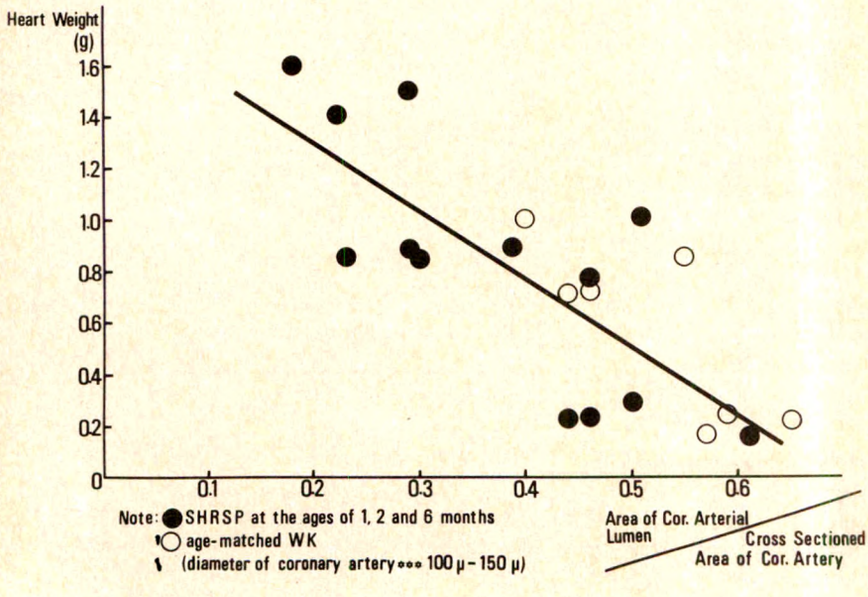

FIGURE 6. Correlation between cardiac and coronary vascular hypertrophy in stroke-prone spontaneously hypertensive rats (SHRSP) and in age-matched normal Wistar-Kyoto (WK) rats. Cor. = coronary.

background, 5 of 22 subjects with borderline hypertension had a left ventricular mass clearly above 2 standard deviations of normal for their age. The blood pressure in these subjects ranged from 126/80 to 134/86 mm Hg, and they showed no other evidence of cardiovascular disease. Similar results in juvenile hypertension were recently also reported by Culpepper et al.[25] More studies are obviously needed, particularly ones with long-term follow-up and correlation with personal and family history for complete correlation of the significance of early increases in left ventricular mass. If documented in man, "cardiac hypertrophy in prehypertension" would have important diagnostic and prognostic implications.

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Hypertrophy in the Denervated Heart: A Comparison of Central Sympatholytic Treatment With 6-Hydroxydopamine and Peripheral Sympathectomy With Nerve Growth Factor Antiserum

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The effects of widespread destruction of central catecholaminergic structures on systemic hemodynamics, ventricular performance, myocardial hypertrophy and the renin-angiotensin system in developing male spontaneously hypertensive rats of the Okamoto strain (SHR) and control normotensive Kyoto Wistar (WKY) rats were examined and contrasted with the effects of peripheral sympathectomy. Both centrally administered 6-hydroxydopamine (6-OHDA) and nerve growth factor antiserum (NGFAS) prevented the development of hypertension in the spontaneously hypertensive rats but did not affect blood pressure in the control rats. Peripheral vascular resistance remained elevated and cardiac and stroke indexes depressed in both 6-OHDA- and NGFAS-treated spontaneously hypertensive rats despite preservation of normal blood pressure. Ventricular performance was depressed in the sham-treated spontaneously hypertensive rats and was not improved by either treatment. Neither 6-OHDA nor NGFAS treatment prevented the development of left ventricular hypertrophy in the spontaneously hypertensive rats despite the decrease in blood pressure. Plasma renin activity was elevated in the 6-OHDA-treated spontaneously hypertensive rats compared with the sham-treated spontaneously hypertensive control rats but was unaffected by treatment with NGFAS.

The data indicate that destruction of central and peripheral noradrenergic structures in the immature spontaneously hypertensive rats prevents the development of hypertension by different physiologic mechanisms but does not alter the suppressed ventricular function, the increased peripheral resistance or the development of myocardial hypertrophy. These results support the concept that increased sympathetic activity is necessary for the development of hypertension in spontaneously hypertensive rats but not for the development of myocardial dysfunction or hypertrophy.

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Our previous studies[1–3] and those of others[4,5] have demonstrated that 6-hydroxydopamine (6-OHDA) administered intraventricularly or intravenously and nerve growth factor antiserum (NGFAS) administered subcutaneously to immature genetically hypertensive rats can prevent hypertension. The first intervention causes selective depletion of central catecholamines; the second, partial peripheral sympathectomy. Preliminary evidence from our laboratories[2] suggests that the two treatments have different effects on systemic hemodynamics, left ventricular performance, myocardial hypertrophy and the renin-angiotensin system. The present study was undertaken to examine and contrast further the effects of widespread destruction of central catecholaminergic structures

with peripheral sympathectomy on systemic hemodynamics, ventricular performance, myocardial hypertrophy and the renin-angiotensin system in developing spontaneously hypertensive rats of the Okamoto strain (SHR) and control normotensive Kyoto Wistar (WKY) rats. Renin activity was measured because it is partially controlled by the sympathetic nervous system and is thought to have independent effects (by way of angiotensin II) on hemodynamics and the development of myocardial hypertrophy.

Methods

Study groups: Fourteen day old male spontaneously hypertensive rats (SHR) or normotensive Kyoto Wistar (WKY) rats (Taconic Farms) were anesthetized with ether, placed in a Kopf stereotaxic holder and treated with intraventricular 6-hydroxydopamine (6-OHDA HBr, Sigma, St. Louis, Missouri) (200 μg free base) as described previously.[1] Control animals received only Merlis solution containing ascorbate. A second group of spontaneously hypertensive and Kyoto Wistar rats were treated with nerve growth factor antiserum (NGFAS) (Burroughs Wellcome) as described previously.[3] Sham-treated spontaneously hypertensive and Kyoto Wistar rats received identical amounts of saline solution.

Hemodynamic measurements: Beginning at 40 days of age, the systolic blood pressure of the conscious rats was measured twice weekly using a modification[1] of the tail cuff method of Pfeffer et al.[6] At 84 days of age 6-OHDA- and sham-treated spontaneously hypertensive and Kyoto Wistar rats and NGFAS- and sham-treated spontaneously hypertensive and Kyoto Wistar rats were anesthetized with pentobarbital sodium (Nembutal®), 50 mg/kg intraperitoneally and hemodynamic studies were performed as previously described.[3] Indexes of ventricular function including peak flow velocity, stroke work and flow acceleration were calculated from the left ventricular pressure and aortic flow tracings as previously described.[8] Cardiac index was calculated from the mean aortic flow tracing. Instantaneous peak flow velocity was calculated by averaging the maximal value of at least 20 phasic flow curves. Immediately after the hemodynamic study the hearts were excised, divided and weighed. The interventricular septum was included with the left ventricle.

Renin and catecholamine measurements: A second group of spontaneously hypertensive and Kyoto Wistar rats were killed at age 84 days by decapitation without anesthesia and exsanguinated. Blood was collected for measurement of plasma renin activity[9] and dopamine-β-hydroxylase activity.[10] The brain minus olfactory bulbs was removed; dissected into telencephalon minus septum and corpus striatum, diencephalon, mid brain and pons-medulla; and stored in liquid nitrogen for catecholamine analysis.[11] The cervicothoracic spinal cord, heart and spleen also were removed and stored in liquid nitrogen for subsequent norepinephrine analysis.[11] The kidneys were removed and stored in liquid nitrogen for renin analysis.[3,12,13] Results were expressed as international units (IU) of renin per gram of kidney.[14]

Results

Blood pressure and heart rate: Systolic hypertension appeared in spontaneously hypertensive rats at about 6 to 8 weeks of age and increased in severity with time (Fig. 1). Treatment with either 6-OHDA or NGFAS prevented the development of hypertension in these rats. The systolic pressures of conscious 6-OHDA- or NGFAS-treated spontaneously hypertensive rats were consistently 5 to 10 mm Hg higher than those of the WKY controls but the difference did not attain statistical significance (Fig. 1). Further, blood pressures of 6-OHDA- or NGFAS-treated and sham-treated WKY rats were not significantly different. Heart rates in conscious 6-OHDA-treated spontaneously hypertensive rats were consistently lower than in vehicle-treated control rats. At the time of sacrifice, the mean heart rate of the 6-OHDA-treated group was 384 ± 17

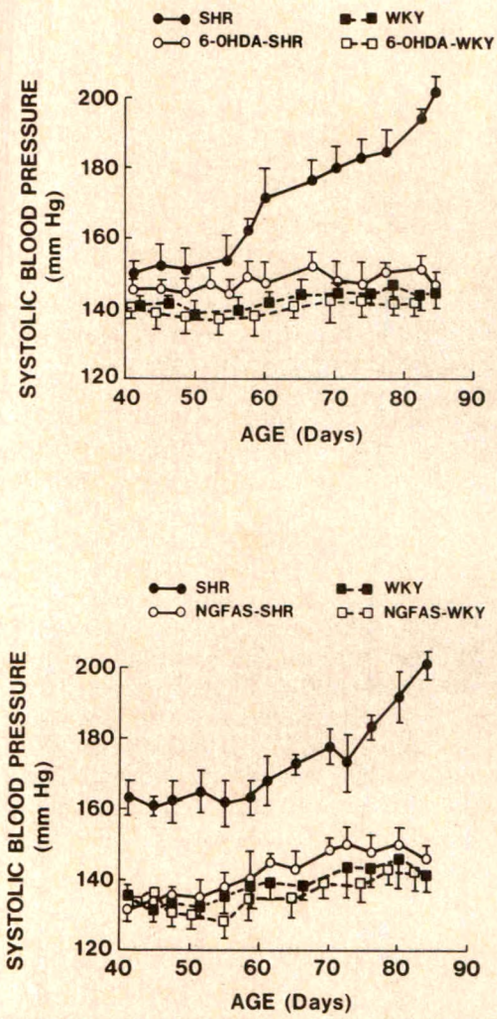


FIGURE 1. Top, systolic blood pressures of unanesthetized 6-hydroxydopamine-(6-OHDA)-treated (O—O) and sham-treated (●—●) spontaneously hypertensive (SHR) rats and 6-OHDA-treated (□—□) and sham-treated (■—■) Kyoto Wistar (WKY) rats plotted against age. Values are expressed as mean ± standard error of the mean. There are eight rats in each group. Systolic pressure of sham-treated spontaneously hypertensive rats at the time of sacrifice was significantly greater than those of the other groups ($P < 0.001$); pressures of the other groups were not significantly different from one another. **Bottom:** systolic blood pressures of unanesthetized nerve growth factor antiserum (NGFAS)-treated (O—O) and sham-treated (●—●) spontaneously hypertensive rats and NGFAS-treated (□—□) and sham-treated (■—■) Kyoto Wistar rats plotted against age. Values are expressed as mean ± standard error of the mean. There are 10 rats in each group. Systolic pressure of sham-treated spontaneously hypertensive rats at the time of sacrifice was significantly greater than those of the other groups ($P < 0.001$); pressures of the other groups were not significantly different from one another.

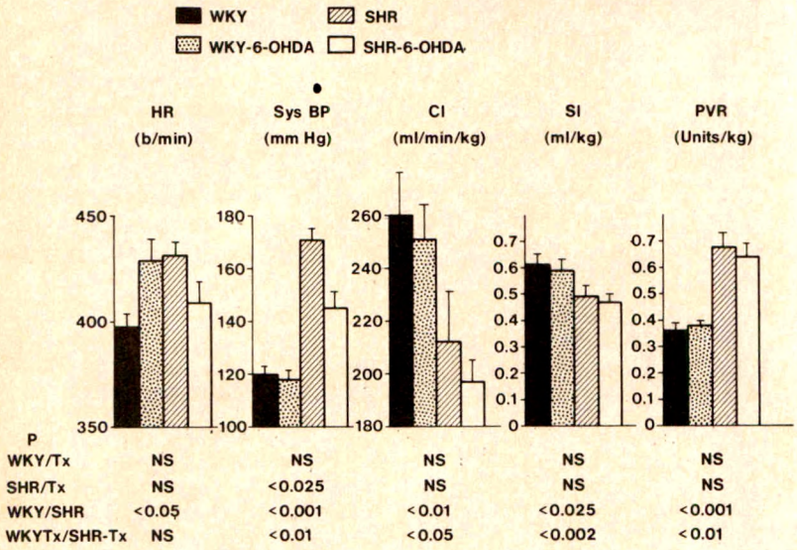


FIGURE 2. Heart rate (HR), peak left ventricular systolic pressure (Sys BP), cardiac index (CI), stroke index (SI) and peripheral vascular resistance (PVR) of the 6-OHDA-treated and sham-treated Kyoto Wistar and spontaneously hypertensive rats. Values are expressed as mean ± standard error of the mean. There were seven rats in each group. Units of peripheral vascular resistance are mm Hg/ml per min. b = beats; NS = not significant; P = probability; Tx = treated; other abbreviations as in Figure 1.

beats/min compared with 438 ± 15 beats/min for the control group ($P < 0.001$). However, at age 12 weeks, the heart rates of sham-treated spontaneously hypertensive rats and 6-OHDA- and sham-treated Kyoto Wistar rats were not significantly different from one another. In the NGFAS studies heart rates in conscious rats at the time of sacrifice were the same in all four experimental groups.

Hemodynamic studies: The data from hemodynamic study of 6-OHDA-and sham-treated spontaneously hypertensive and Kyoto Wistar rats performed under pentobarbital anesthesia are summarized in Figure 2. Heart rates of sham-treated spontaneously hypertensive rats were significantly greater than those of sham-treated Kyoto Wistar rats. Six-hydroxydopamine treatment tended to lower heart rate in the spontaneously hypertensive rats but the difference did not attain statistical significance; treatment did not alter heart rate in the Kyoto Wistar rats. Left ventricular systolic pressures recorded in anesthetized rats were lower than pressures in conscious rats for all groups. Pressures of vehicle-treated spontaneously hypertensive rats were significantly higher than those of 6-OHDA-treated spontaneously hypertensive rats and of both 6-OHDA- and vehicle-treated Kyoto Wistar rats. Systolic pressures of 6-OHDA-treated spontaneoulsy hypertensive rats remained significantly higher than those of either vehicle-treated or 6-OHDA-treated Kyoto Wistar rats. These findings contrast with blood pressure data obtained from conscious animals in which systolic pressures of 6-OHDA-treated spontaneously hypertensive rats were indistinguishable from those of Kyoto Wistar control rats.

Cardiac indexes of the 6-OHDA- and vehicle-treated spontaneously hypertensive rats were significantly lower than those of both Kyoto Wistar treatment

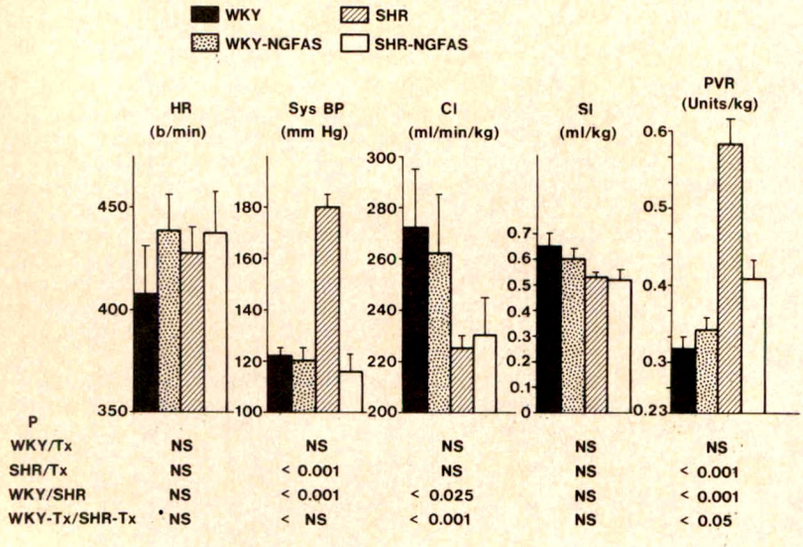


FIGURE 3. Heart rate (HR), peak left ventricular systolic pressure (Sys BP), cardiac index (CI), stroke index (SI) and peripheral vascular resistance (PVR) of the NGFAS-treated and sham-treated Kyoto Wistar and spontaneously hypertensive rats. Values are expressed as mean ± standard error of the mean. There are seven rats in each group. Units of peripheral vascular resistance are expressed as mm Hg/ml per min. Unidentified abbreviations as in Figures 1 and 2.

groups. Treatment with 6-OHDA did not significantly alter the cardiac index in either strain, although treated rats tended to have a lower cardiac index than sham-treated control rats. Similarly, stroke indexes of both groups of spontaneously hypertensive rats were consistently lower than those of both groups of Kyoto Wistar rats, but 6-OHDA treatment did not alter the stroke index in either strain.

The calculated peripheral vascular resistance in both vehicle-treated and 6-OHDA-treated spontaneously hypertensive rats was significantly higher than in either group of Kyoto Wistar control rats and was not altered by 6-OHDA treatment. The apparent persistence of elevated peripheral vascular resistance in the spontaneously hypertensive rats after 6-OHDA treatment despite the decrease in blood pressure may reflect either a fixed peripheral vascular abnormality or the depressed cardiac output found in both treated and sham-treated spontaneously hypertensive rats. The intact peripheral sympathetic nervous system and elevated plasma renin activity found in 6-OHDA-treated animals might also contribute to elevations in peripheral vascular resistance.

Hemodynamic data from pentobarbital anesthetized NGFAS- and sham-treated animals are summarized in Figure 3. In contrast to 6-OHDA treatment administration of NGFAS did not alter heart rate, which was not significantly different among the four experimental groups. Left ventricular systolic pressures of NGFAS-treated spontaneously hypertensive rats were indistinguishable from those of both Kyoto Wistar groups. These data are similar to those obtained in conscious rats (although absolute values recorded in all groups of conscious animals were uniformly higher) but contrast with those obtained in anesthetized 6-OHDA-treated spontaneously hypertensive rats, in which systolic pressures remained significantly higher than in the Kyoto Wistar strain. Cardiac and stroke indexes were not affected by NGFAS treatment. Both values tended to be depressed in spontaneously hypertensive rats compared with Kyoto Wistar control rats, but differences in stroke index did not attain statistical significance. In contrast to 6-OHDA treatment, administration of NGFAS did result in a significant reduction in peripheral vascular resistance. Calculated peripheral vascular resistance in the normotensive NGFAS-treated spontaneously hypertensive rat remained significantly greater than in the Kyoto Wistar strain, reflecting either a peripheral vascular abnormality or the depressed cardiac output found in the spontaneously hypertensive rat.

Ventricular function as reflected in peak flow velocity and flow acceleration (dF/dt) was depressed in both groups of spontaneously hypertensive rats compared with values in the Kyoto Wistar strain (Fig. 4). Treatment with 6-OHDA did not alter ventricular function in either strain. In contrast, left ventricular work, which was calculated by multiplying stroke work by heart rate, was not significantly different in the vehicle-treated spontaneously hypertensive rat and the Kyoto Wistar rat. Treatment with 6-OHDA caused a decrease in left ventricular work, presumably by lowering systemic pressure. Unlike 6-OHDA treatment, administration of NGFAS was associated with depression of ventricular performance. This effect was more marked in the spontaneously hypertensive rat than in the Kyoto Wistar rat. NGFAS treatment caused a more marked decrease in left ventricular work than did 6-OHDA, probably because it altered both systemic pressure and ventricular function.

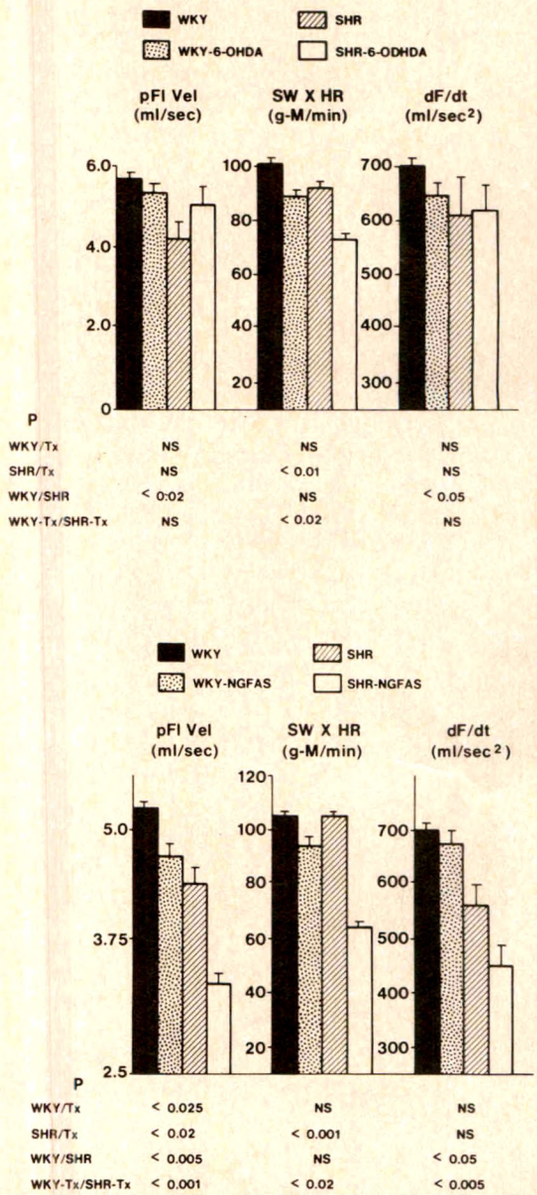
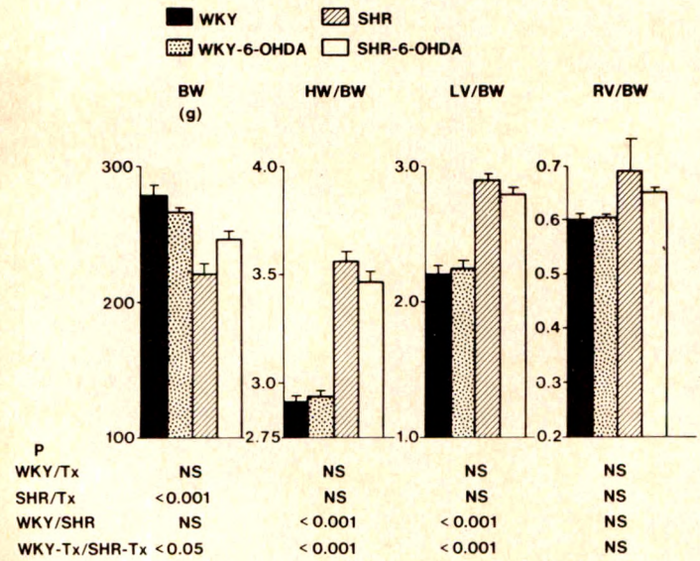


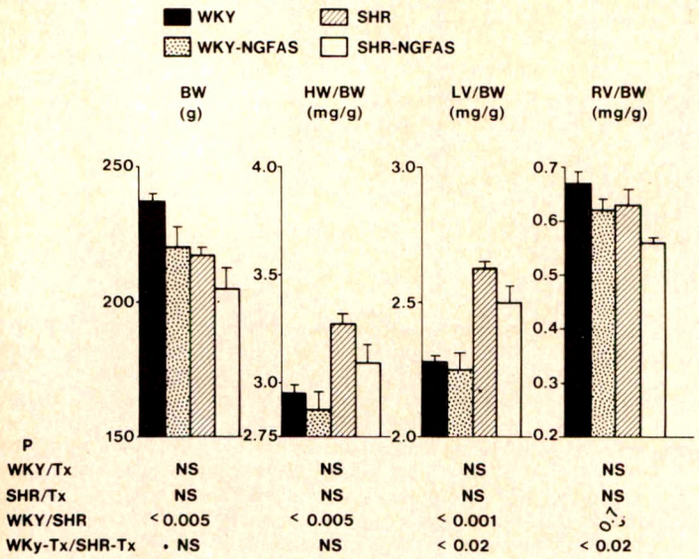
FIGURE 4. Top, peak flow velocity (pFl Vel), product of stroke work and heart rate (SWxHR) and flow acceleration (dF/dt) of the 6-OHDA-treated and sham-treated Kyoto Wistar and spontaneosuly hypertensive rats. Values are expressed as mean ± standard error of the mean. There are seven rats in each group. **Bottom;** peak flow velocity (pFl Vel), product of stroke work and heart rate (SWxHR) and flow acceleration (dF/dt) of the NGFAS-treated and sham-treated Kyoto Wistar and spontaneously hypertensive rats. Values are expressed as mean ± standard error of the mean. There are seven rats in each group. Unidentified abbreviations as in Figures 1 and 2.

Ventricular hypertrophy: The development of left ventricular hypertrophy in the spontaneously hypertensive rat was not affected by 6-OHDA treatment despite the lowering of blood pressure. The heart weight/body weight ratio, left ventricular weight/body weight ratio and right ventricular weight/body weight ratio were the same in 6-OHDA and vehicle-treated spontaneously hypertensive rats (Fig. 5, Top panel). Heart weight/body weight and left ventricular weight/body weight ratios were significantly greater in both groups of spontaneously hypertensive rats than in the two Kyoto Wistar groups. Similar results were obtained in NGFAS-treated animals (Fig. 5, bottom panel). Table I shows that 6-OHDA-treated and NGFAS-treated spontaneously hypertensive rats and their sham-treated controls did not differ from one another in absolute left ventricular weight, ribonucleic acid (RNA), deoxyribonucleic acid (DNA) and OH-proline concentration or RNA, DNA and OH-proline content.

Renin and catecholamine activity: Plasma renin activity was significantly elevated in the 6-OHDA-treated spontaneously hypertensive rat but not in the 6-OHDA-treated Kyoto Wistar rat (Table II). Circulating renin tended to be higher in the sham-treated Kyoto Wistar strain than in the spontaneously hypertensive rat, but the difference did not attain statistical significance. Kidney renin content was unaltered by 6-OHDA treatment in both strains. Plasma dopamine β-hydroxylase activity was the same in the sham-treated spontaneously hypertensive rats and Kyoto Wistar rats and was not affected by 6-OHDA treatment. In contrast, NGFAS tretment did not affect plasma renin



P	BW	HW/BW	LV/BW	RV/BW
WKY/Tx	NS	NS	NS	NS
SHR/Tx	<0.001	NS	NS	NS
WKY/SHR	NS	<0.001	<0.001	NS
WKY-Tx/SHR-Tx	<0.05	<0.001	<0.001	NS



P	BW	HW/BW	LV/BW	RV/BW
WKY/Tx	NS	NS	NS	NS
SHR/Tx	NS	NS	NS	NS
WKY/SHR	<0.005	<0.005	<0.001	<0.02
WKy-Tx/SHR-Tx	• NS	NS	<0.02	<0.02

FIGURE 5. Top, body weight (BW), heart weight/body weight ratio (HW/BW), left ventricular/body weight ratio (LV/BW) and right ventricular/body weight ratio (RV/BW) of 6-OHDA- and sham-treated Kyoto Wistar and spontaneously hypertensive rats. Values are expressed as mean ± standard error of the mean. There are eight rats in each group. **Bottom,** the same variables in NGFAS- and sham-treated Kyoto Wistar and spontaneously hypertensive rats. Values are expressed as mean ± standard error of the mean. There are seven rats in each group. Unidentified abbreviations as in Figures 1 and 2.

TABLE I

Effects of 6-OHDA and NGFAS Administration on Left Ventricular Weight and RNA, DNA, and OH-Proline in the Spontaneously Hypertensive Rat

		RNA		DNA		OH-Proline	
	LV Weight (mg)	Concentration (μg/mg)	Content (μg)	Concentration (μg/mg)	Content (μg)	Concentration (μg/mg)	Content (μg)
6-OHDA (no. = 8)	688 ± 22	3.03 ± 0.04	2084 ± 64	1.75 ± 0.08	1204 ± 35	0.75 ± 0.03	516 ± 18
Vehicle (no. = 5)	634 ± 34	3.08 ± 0.07	1953 ± 53	1.79 ± 0.06	1134 ± 59	0.80 ± 0.04	507 ± 13
P	NS	NS	NS	NS	NS	NS	NS
NGFAS (no. = 9)	639 ± 28	3.01 ± 0.03	1923 ± 67	1.80 ± 0.05	1150 ± 47	0.78 ± 0.04	498 ± 15
Vehicle (no. = 9)	656 ± 42	3.07 ± 0.04	2014 ± 86	1.69 ± 0.07	1109 ± 34	0.81 ± 0.03	531 ± 18
P	NS	NS	NS	NS	NS	NS	NS

Results are expressed as mean ± standard error of the mean.
DNA = deoxyribonucleic acid; NGFAS = nerve growth factor antiserum; no. = number of rats; NS = not significant; *P* = probability; RNA = ribonucleic acid; 6-OHDA = 6-hydroxydopamine.

activity but was associated with elevated kidney renin content in the spontaneously hypertensive rats. No effect was seen in the Kyoto Wistar strain. Plasma dopamine β-hydroxylase activity was significantly lower in NGFAS-treated spontaneously hypertensive rats than in their controls, consistent with the known inhibitory effect of NGFAS on the development of the sympathetic nervous system. A similar effect was seen in the Kyoto Wistar strain but did not attain statistical significance.

Catecholamine concentrations in various regions of brain, spinal cord, myocardium and spleen of 6-OHDA-treated and control animals are summarized in Table III. Treated spontaneously hypertensive rats showed a 99 percent decrease in telencephalic (whole telencephalon-septum and striatum) norepinephrine and 61, 48 and 34 percent decreases in norepinephrine in the diencephalon, mid brain and pons-medulla, respectively. Spinal cord norepinephrine was depleted by 96 percent in treated animals. Percent changes were similar in the Kyoto Wistar rats. Myocardial and splenic norepinephrine concentration were the same in 6-OHDA-treated spontaneously hypertensive rats and Kyoto Wistar rats as in vehicle-treated control rats.

NGFAS treatment did not affect regional brain or spinal cord norepinephrine concentrations in either

TABLE II

Effects of 6-OHDA and NGFAS Administration to Spontaneously Hypertensive (SHR) and Kyoto Wistar (WKY) Rats on Renin and Dopamine Beta-Hydroxylase (DBH)

	Systolic Blood Pressure (mm Hg)	Plasma Renin Activity (ng AI/ml per hour)	Kidney Renin Content (IU/g)	Plasma DBH Activity (μmol/liter per min)
SHR				
6-OHDA (no. = 10)	147 ± 3	6.3 ± 1.8	2.4 ± 0.38	0.94 ± 0.06
Vehicle (no. = 9)	202 ± 4	1.7 ± 0.6	2.3 ± 0.21	0.82 ± 0.07
P	<0.001	<0.01	NS	NS
NGFAS (no. = 8)	150 ± 3	1.5 ± 0.7	5.2 ± 0.51	0.58 ± 0.05
Vehicle (no. = 8)	200 ± 4	1.8 ± 0.5	2.2 ± 0.30	0.91 ± 0.06
P	<0.001	NS	<0.001	<0.02
WKY				
6-OHDA (no. = 11)	141 ± 3	2.9 ± 1.0	3.4 ± 0.23	0.79 ± 0.08
Vehicle (no. = 8)	144 ± 4	2.5 ± 0.8	3.1 ± 0.34	0.69 ± 0.05
P	NS	NS	NS	NS
NGFAS (no. = 8)	142 ± 4	3.4 ± 2.2	2.9 ± 0.3	0.65 ± 0.05
Vehicle (no. = 6)	146 ± 5	2.3 ± 0.3	3.0 ± 0.2	0.72 ± 0.06
P	NS	NS	NS	NS

Results are expressed as mean ± standard error of the mean. Abbreviations as in Table I.

TABLE III

Effects of 6-OHDA and NGFAS Administration to Spontaneously Hypertensive (SHR) and Kyoto Wistar (WKY) Rats on Tissue Catecholamine Levels

	Norepinephrine (μg/g)						
	Telencephalon	Diencephalon	Mid Brain	Pons-Medulla	Spinal Cord	Heart	Spleen
SHR							
6-OHDA (no. = 10)	0.002 ± 0.001	0.228 ± 0.041	0.220 ± 0.040	0.257 ± 0.018	0.006 ± 0.002	0.653 ± 0.061	0.264 ± 0.07
Vehicle (no. = 9)	0.243 ± 0.010	0.585 ± 0.062	0.459 ± 0.031	0.385 ± 0.024	0.161 ± 0.013	0.584 ± 0.082	0.279 ± 0.06
P	<0.001	<0.001	<0.001	<0.001	<0.001	NS	NS
NGFAS (no. = 8)	0.241 ± 0.015	0.554 ± 0.103	0.436 ± 0.012	0.380 ± 0.020	0.183 ± 0.016	0	0
Vehicle (no. = 8)	0.253 ± 0.010	0.576 ± 0.097	0.448 ± 0.025	0.365 ± 0.048	0.173 ± 0.018	0.593 ± 0.065	0.265 ± 0.09
P	NS	NS	NS	NS	NS	<0.001	<0.001
WKY							
6-OHDA (no. = 11)	0.003 ± 0.001	0.225 ± 0.023	0.161 ± 0.010	0.157 ± 0.015	0.010 ± 0.003	0.552 ± 0.032	0.274 ± 0.02
Vehicle (no. = 8)	0.261 ± 0.017	0.571 ± 0.064	0.320 ± 0.013	0.235 ± 0.018	0.151 ± 0.012	0.519 ± 0.043	0.281 ± 0.03
P	<0.001	<0.001	<0.001	<0.001	<0.001	NS	NS
NGFAS (no. = 8)	0.243 ± 0.016	0.583 ± 0.053	0.316 ± 0.032	0.217 ± 0.010	0.153 ± 0.009	0.015 ± 0.003	0
Vehicle (no. = 6)	0.259 ± 0.014	0.527 ± 0.041	0.301 ± 0.025	0.229 ± 0.021	0.162 ± 0.015	0.536 ± 0.078	0.276 ± 0.04
P	NS	NS	NS	NS	NS	<0.001	<0.001

Results are expressed as mean ± standard error of the mean. Abbreviations as in Table I.

spontaneously hypertensive or Kyoto Wistar rats (Fig. 3). However, it did cause profound depletions of myocardial and splenic norepinephrine, compatible with sympathetic denervation.

Discussion

Development of myocardial hypertrophy despite prevention of hypertension: This study has shown that either destruction of central noradrenergic structures or peripheral sympathectomy can prevent the development of hypertension in the maturing spontaneously hypertensive rat. These interventions do not alter blood pressure in normotensive Kyoto Wistar control animals, indicating that they do not have nonspecific hypotensive effects but that they interfere selectively with processes critical to the development of hypertension in the spontaneously hypertensive rat. Further, although both interventions lower the arterial pressure of the conscious spontaneously hypertensive rat into the normal range, neither is fully effective in preventing the increased peripheral resistance and depressed cardiac index and left ventricular performance characteristic of the untreated spontaneously hypertensive rat. In both 6-OHDA- and NGFAS-treated spontaneously hypertensive rats myocardial hypertrophy develops to the same extent as in vehicle-treated control rats in the presence of systolic blood pressure levels only 5 to 10 mm Hg higher than those of Kyoto Wistar rats of the same age. These observations suggest that the hemodynamic abnormalities and myocardial hypertrophy seen in the spontaneously hypertensive rat may be determined by factors independent of the blood pressure.

Cardiovascular function in treated rats: We observed major differences between the effects of centrally administered 6-OHDA and of NGFAS on cardiovascular function in the young spontaneously hypertensive rat. Although both interventions lowered the systolic pressures of conscious spontaneously hypertensive rats (tail cuff method) into the normal (Kyoto Wistar) range, systolic pressures of 6-OHDA-treated spontaneously hypertensive rats measured under pentobarbital anesthesia were significantly higher than those of NGFAS-treated spontaneously hypertensive rats and of Kyoto Wistar rats. In addition 6-OHDA lowered heart rate in conscious spontaneously hypertensive rats but not in pentobarbital-anesthetized animals. These observations suggest that barbiturate anesthesia has a pressor effect in the 6-OHDA-treated spontaneously hypertensive rat that is not seen in Kyoto Wistar rat or in the spontaneously hypertensive rat that has been sham-treated or subjected to partial peripheral sympathectomy with NGFAS. The mechanism of this effect is unknown but may relate to the destruction of central inhibitory vasomotor pathways by 6-OHDA. This anomalous response to anesthesia must be considered in the evaluation of hemodynamic data in the 6-OHDA-treated spontaneously hypertensive rat.

Cardiac index, stroke index and calculated peripheral vascular resistance were not altered by 6-OHDA treatment in either the spontaneously hypertensive or the Kyoto Wistar rat despite the decrease in blood pressure. These findings may reflect either a fixed structural or functional abnormality, or both, of resistance vessels or depressed left ventricular function in the spontaneously hypertensive rat. These experiments

do not permit us to assess the contributions of the intact peripheral sympathetic nervous system and of elevated plasma renin activity to elevations in peripheral vascular resistance in the 6-OHDA-treated spontaneously hypertensive rat. Peripheral vascular resistance in both 6-OHDA- and vehicle-treated spontaneously hypertensive rats was twice that of the Kyoto Wistar rat. Persistent elevations in peripheral vascular resistance were also observed in the NGFAS-treated spontaneously hypertensive rat but were smaller in magnitude (25 percent greater than in the Kyoto Wistar rat) than in the 6-OHDA-treated animal. The partial reduction in peripheral vascular resistance seen in the NGFAS-treated spontaneously hypertensive rat probably represents the direct effect of immunosympathectomy on the resistance vessels.

Persistence of increased peripheral vascular resistance in treated rats: Evidence for peripheral vascular abnormalities in the spontaneously hypertensive rat that cannot be fully accounted for by increased sympathetic activity or increased systemic pressure has been adduced by Folkow et al.[15] They demonstrated hemodynamic changes characteristic of hypertrophy in the hindlimb vasculature of 8 month old spontaneously hypertensive rats that had been treated in infancy with NGFAS. The resistance changes were present even in rats that had minimal elevations in resting pressure. The investigators concluded that the resistance vessels of the spontaneously hypertensive rat might for genetic reasons be more likely to manifest structural abnormalities in response to small increases in pressure than the resistance vessels of normotensive control rats. Other investigators have observed enhanced responsiveness to vasoconstrictur stimuli in the spontaneously hypertensive rat[16] and the renal hypertensive rat[17] before or concomitant with the development of hypertension. Experiments in coarctation hypertension in which hindlimb vascular beds are protected from the increase in arterial pressure by constricting the aorta have shown increased resting resistance, enhanced vascular responsiveness to pressor agents and impaired maximal vasodilation in hindlimb vessels.[18,19] Taken together, these observations are compatible with the notion that abnormalities in the walls of resistance vessels in hypertensive animals are not entirely the direct result of elevated arterial pressure. This may in part explain the persistence of increased peripheral vascular resistance in our 6-OHDA- and NGFAS-treated spontaneously hypertensive rats.

Ventricular performance in treated rats: The effects of 6-OHDA and NGFAS treatment on ventricular performance in the spontaneously hypertensive rat were different. Six hydroxydopamine treatment did not alter either ventricular peak flow velocity or flow acceleration in the spontaneously hypertensive or the Kyoto Wistar strain; NGFAS clearly depressed ventricular performance in the spontaneously hypertensive rat and may have had a small depressant effect in the Kyoto Wistar rat as well. These observations suggest that left ventricular function in the resting pentobarbital-anesthetized spontaneously hypertensive rat is maintained in part by increased sympathetic activity that can be removed by immunosympathectomy but not by ablation of central noradrenergic pathways. In contrast, both 6-OHDA and NGFAS treatment caused decreases in left ventricular function.

Hypothesis to explain impaired myocardial function and ventricular hypertrophy when hypertension is prevented by treatment of the spontaneously hypertensive rat: The findings of depressed myocardial performance and left ventricular hypertrophy in the treated spontaneously hypertensive rat in the absence of systemic hypertension suggest that these abnormalities may not be entirely secondary to the hypertension but rather are related to some underlying myocardial abnormality. However, the persistence of increased peripheral vascular resistance in all spontaneously hypertensive rat groups raises the possibility that the reduced ventricular peak flow velocity and flow acceleration could in part be related to this rather than to primary myocardial dysfunction. We have previously postulated that a myocardial abnormality occurs in the animal genetically predisposed to hypertension and plays a role in the pathogenesis of the syndrome.[20] According to our hypothesis diminished cardiac output secondary to depressed myocardial function may lead to a compensatory increase in sympathetic activity. The enhanced sympathetic activity could result in systemic vasoconstriction and increased peripheral vascular resistance, eventually leading to systemic hypertension despite the impaired myocardial performance. Consistent with this hypothesis is the demonstration that the prevention of hypertension by procedures such as administration of 6-OHDA or NGFAS, which have different physiologic consequences, did not alter either myocardial performance or the development of myocardial hypertrophy in the spontaneously hypertensive rat. A possible biochemical basis for impaired contractility is the abnormal calcium transport by the sarcoplasmic reticulum of the left ventricular myocardium, which was recently demonstrated in the spontaneously hypertensive rat.[21] Confirmation of this observation and systematic exploration of other mechanisms that regulate myocardial contractility in the spontaneously hypertensive rat are needed before our hypothesis can be rigorously tested.

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Cardiac Pumping Ability in Rats With Experimental Renal and Genetic Hypertension

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In two experimental models of established hypertension in the rat (two kidney, one clip renal and genetic hypertension), the maximum by which stroke volume and cardiac output could be increased during an acute preload stress was significantly reduced despite the concomitant development of left ventricular hypertrophy. Reversal of cardiac hypertrophy by prolonged treatment with methyldopa (range 3 to 6 weeks) during the established phase of spontaneous hypertension normalized arterial blood pressure and improved ventricular pumping ability. The improved performance was in part due to reduced impedance to ventricular ejection because it did not persist when peripheral resistance was increased by an acute administration of phenylephrine hydrochloride. Thus, hemodynamic as well as structural factors contribute to alterations in cardiac function during the chronic established phase of arterial hypertension.

Recent characterization of the hemodynamic abnormalities accompanying the evolution of arterial hypertension shows promise for understanding the nature of the mechanisms responsible for the ultimate elevation of arterial pressure. For example, the description of a hyperkinetic circulatory syndrome brought about by an increase in cardiac output due to tachycardia is currently considered a prerequisite for the later occurrence of sustained hypertension in man.[1] There is some experimental evidence to support this view.[2] Animals with evolving hypertension of either renal[3–5] or genetic[6] origin show a phase of increased cardiac output preceding by days, weeks or even months the pronounced increase in peripheral resistance characteristic of the established forms of arterial hypertension.

The reason for an apparent dependence of the elevated arterial pressure first on increased cardiac output and second on augmented peripheral resistance is not understood. One view[7] holds that the early increase in cardiac output causes resistance vessels to constrict in an attempt to autoregulate blood flow. Another view[8] suggests that changes in cardiac output may result from a primary increase in cardiac performance brought about by activation of the renin-angiotensin system or alterations in cardiac autonomic drive, or both.

So far there is no agreement as to which view is correct; details of the problems and the arguments with each theory were the subject of a recent review.[2] Here it suffices to say that although it is unlikely that the heart plays a direct role in the initiation of hypertension, it does appear to influence the characteristics of hypertension as well as to suffer from its effects. This subject has been of recent interest particularly because cardiac involvement in hypertension is characterized by structural modifications that result in the development of left ventricular hypertrophy. Unfortunately, the effect of increased cardiac mass on pump function is not well established even though it is generally acknowledged that the increase in left ventricular wall thickness tends to normalize the stress imposed by the elevation in afterload. This report reviews our findings[8–11] regarding: (1) the changes in cardiac performance associated

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with the presence of myocardial hypertrophy during the established phase of experimental hypertension in two rat models; (2) the effects of long-term antihypertensive therapy on cardiac hypertrophy and pump function in the rat with genetic hypertension; and (3) the possible relations among hemodynamic factors, ventricular function and the presence of cardiac hypertrophy.

Methods

Volume-output-pressure curves to evaluate cardiac mechanical performance: The pumping ability of the heart was evaluated from the curves describing the relation of stroke volume and cardiac output to left ventricular end-diastolic pressure. Strictly considered, these curves are not Frank-Starling curves relating energy of contraction to length of muscle fibers but curves that provide only an index of pump performance.[12] Changes in mechanical performance are construed from the maximal levels of stroke volume and cardiac output reached during an acute increase in the preload. The validity and limitations of this method as an index of global cardiac mechanical performance are detailed elsewhere[7,13,14]; however, these curves are inadequate for judging changes in ventricular contractility.

Experimental techniques: *A brief description of the techniques employed follows.* Rats were anesthetized with ether and ventilated with a mechanical respirator (Harvard Apparatus, model 681) by way of a cannula (PE–205, Clay Adams, New Jersey) inserted into the trachea. Arterial, left ventricular and right atrial pressures were obtained from solid state transducers connected to catheters placed in the right carotid artery (PE–10) and the jugular vein (PE–50), respectively. The fluid-filled catheter transducer systems have a natural resonant frequency of 83 hertz and a damping coefficient of 0.57. An additional catheter (PE–50) was advanced into the inferior vena cava by way of a femoral vein for infusion or withdrawal of blood. Aortic blood flow was measured with an electromagnetic flow transducer placed around the ascending aorta (SP–2202 Gould, Inc., Statham Division, Oxnard, California). Zero aortic blood flow was defined as the flat portion of the flow curve at the end of the diastolic period; its accuracy was confirmed after cessation of cardiac activity at the end of the experiment. The electric signal from the flowmeter was fed into an analog integrator (model 4307–05, Gould Inc., Cleveland, Ohio) to obtain beat by beat values of stroke volume and into a tachometer (model 4307–13, Gould, Inc., Cleveland, Ohio) to display beat by beat variations in cardiac rate. The electronic circuitry employed in these experiments has previously been described.[8] Peripheral vascular resistance was calculated as the ratio of mean arterial pressure (in mm Hg) to cardiac output (in ml/min) multiplied by 100.

Baseline hemodynamic values were recorded for a minimum of 10 minutes after all surgical manipulations were completed and after the animals were judged to be in a steady state level of anesthesia. The aortic catheter was advanced into the left ventricle to record left ventricular systolic and end-diastolic pressures.

Ventricular pumping ability was determined by rapidly altering venous return by a combination of bleeding and reinfusion of the blood taken plus an additional 10 ml obtained from a donor animal. Instantaneous changes in right atrial and left ventricular pressures, stroke volume and cardiac output were recorded continuously throughout the test period and analyzed by averaging individual values of five consecutive beats at 3 second intervals throughout the study. The averages of stroke volume and cardiac output were then plotted along the entire range of increasing end-diastolic pressures to ascertain both the rate of change and the peak values of ejection variables due to increased cardiac inflow (preload stress).

Technique for determining organ weight: When all experiments were completed, the heart was carefully removed and cleaned. Total heart weight was determined after all major vessels were removed. The atria were cut free to obtain total ventricular weight. Left ventricular weight was also determined after the free right ventricular wall was removed, leaving the interventricular septum intact.

Study animals: The studies were performed in rats with established hypertension of either renal or genetic origin. Fourteen rats served as the renal model of two kidney, one clip experimental hypertension after the arterial pressure had been elevated for an average of 9 weeks.[8] Twenty other normal American Wistar rats served as sham-operated control animals. The other model of experimental hypertension consisted of 13 rats with spontaneous hypertension (Charles Rivers, Wilmington, Massachusetts) studied at an age of 17 to 24 weeks.[11] Their normotensive control animals were 10 Wistar-Kyoto rats of similar age and weight obtained from Taconic Farms (Germantown, New York).

Treatment protocol: In a separate experiment 36 other rats with spontaneous hypertension were given methyldopa for a period of time sufficient to correct their hypertension and produce reversal of cardiac hypertrophy.[11] For at least 2 weeks preceding the administration of the drug and throughout the duration of therapy, systolic blood pressure was measured twice weekly by a tail-cuff method.[15] Powdered methyldopa (Aldomet®) was dissolved in deionized water and given in place of normal drinking water for either 3 or 6 weeks. Although the initial concentration was about 2.5 g/liter, it was necessary to increase the dosage to between 3.0 and 5.0 g/liter to overcome drug tolerance. The sole criterion for the increase in drug concentration during the treatment periods was the maintenance of systolic blood pressure at or near normotensive levels.

Results

Characteristics of cardiac performance in rats with established renal hypertension: In rats with the established form of two kidney, one clip hypertension, after anesthesia was administered and the chest opened, mean arterial pressure averaged 134 ± 8 mm Hg compared with 84 ± 4 mm Hg ($P < 0.001$) in normotensive American Wistar rats.[8] Hemodynamic monitoring with an electromagnetic flowmeter confirmed that the elevation in arterial pressure was due to increased peripheral resistance (423 ± 36 units [(mm Hg/ml per min) × 100]/kg in the hypertensive versus 247 ± 16 units/kg in the normotensive rats); heart rate, stroke volume and cardiac output were essentially the same in both hypertensive and normotensive rats. However, resting levels of end-diastolic pressure tended to be above normal in the rats with renal hypertension (5.9 ± 0.8 versus 4.7 ± 0.4 mm Hg), but the difference was not statistically significant ($P > 0.05$).

In the hypertensive group the ratio of total heart weight to body weight was significantly above the values in rats without renal arterial constriction (3.70 ± 0.10 compared with 2.57 ± 0.06 mg/g) ($P < 0.001$). The increase in cardiac weight was partly due to a 13 percent

increase in tissue water; however, the significant decrease in deoxyribonucleic acid (DNA) concentration found in the hearts of hypertensive rats indicates the presence of hypertrophy rather than hyperplasia.[8]

Pressure-flow curves obtained in 12 of the 20 normal rats and 11 of the 14 renal hypertensive rats revealed that the established phase of benign renal hypertension was associated with a moderate decrease in peak pumping ability as determined by changes in ventricular stroke volume and cardiac output function curves.

With respect to cardiac output, as left ventricular end-diastolic pressure increased from 2.0 to about 10.0 mm Hg, significantly lesser ($P < 0.001$) quantities of blood were delivered into the systemic circulation by the hypertrophied heart of renal hypertensive rats (Fig. 1). In addition, plateau values for cardiac output were below those measured in normotensive rats at matched left ventricular end-diastolic pressures. At end-diastolic pressures greater than 16.0 mm Hg, cardiac output in renal hypertensive rats decreased sharply in a manner reminiscent of that of a descending limb of a Frank-Starling curve. A descending limb could not be obtained at these higher rates of venous inflow in normotensive rats despite loading with equal amounts of blood. Finally, the reduction in cardiac output during both the ascending and plateau portions of the curve in rats with renal hypertension seems not to depend on differences in heart rate or arterial pressure. Normal and hypertensive rats responded to the variations in venous return with comparable changes in both pressure and heart rate (see Table III in Reference 8).

Features of cardiac pumping ability in the established phase of spontaneous hypertension: The established phase of spontaneous hypertension was accompanied by significant cardiac hypertrophy with the left ventricular to body weight ratio averaging 2.64 ± 0.03 mg/g in spontaneously hypertensive rats and 2.23 ± 0.05 mg/g ($P < 0.001$) in a normotensive control group of Wistar-Kyoto rats.[11] Hemodynamically, spontaneously hypertensive rats displayed an increased peripheral resistance and reduced stroke volume and cardiac output. Differences were more pronounced when expressed in terms of stroke and cardiac indexes (Fig. 2), which corrected for variations in body weight (349 ± 7 g in hypertensive versus 327 ± 6 g in normotensive rats).

Figure 3 shows the ventricular output curve during rapid intravenous infusion of blood in spontaneously hypertensive rats. The maximal cardiac output at the plateau of the ventricular function curve was depressed, there being a −34 percent difference in peak cardiac output between normotensive and hypertensive rats. The stroke volume and stroke volume per kilogram of body weight (stroke index) at the plateau of the function curve was also lower than that obtained in normotensive rats[11] (stroke volume: 0.35 ± 0.01 versus 0.46 ± 0.01 ml, and stroke index: 0.91 ± 0.09 versus 1.40 ± 0.03 ml/kg, respectively). Peak stroke work averaged 75 ± 4 g·cm in hypertensive rats compared with 70 ± 3 g·cm in normotensive control rats ($P > 0.05$).

During preload stress the heart rate decreased and arterial pressure increased in both strains of hypertensive and normotensive rats. In the former the cardiac rate decreased from 357 ± 10 to 295 ± 4 beats/min at the plateau of the function curve. During the same period left ventricular systolic pressure increased from 140 ± 6 to 151 ± 4 mm Hg. In the normotensive rats the heart rate decreased from 395 ± 10 to 353 ± 8 beats/min and systolic pressure increased from 107 ± 3 to 120 ± 2 mm Hg.

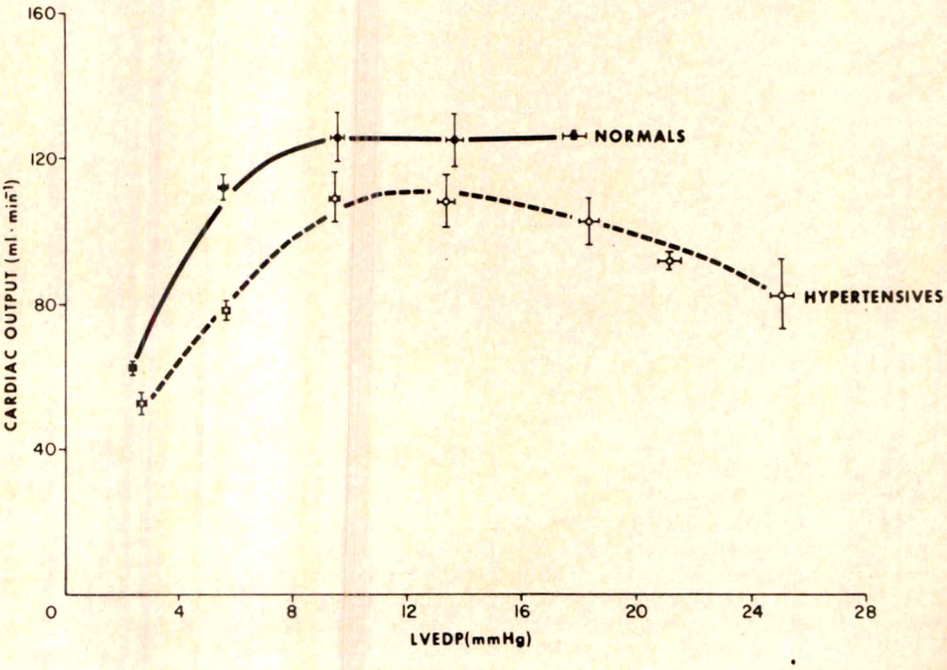

FIGURE 1. Left ventricular cardiac output function curves in normal (**solid line**) and renal hypertensive rats (**broken line**). At matched left ventricular end-diastolic pressures (LVEDP) ranging from 4 to 18 mm Hg, hypertensive rats manifest a moderate decrease in pumping ability suggestive of left ventricular dysfunction. The occurrence of the descending limb at pressures greater than 18 mm Hg suggests the appearance of acute cardiac failure. (Reprinted from Averill et al.,[8] by permission of the American Heart Association, Inc.)

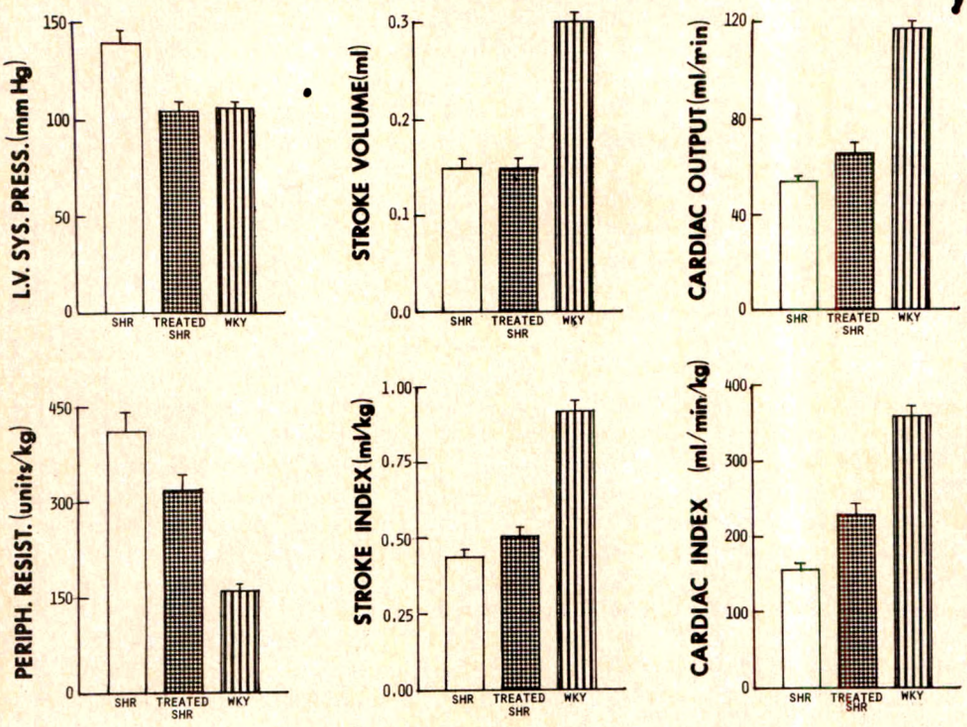

FIGURE 2. Baseline hemodynamic values in untreated (**clear bar**) and treated (**dotted bar**) spontaneously hypertensive rats (SHR) are contrasted with those in normotensive Wistar-Kyoto (WKY rats) (**striped bar**). In animals given methyldopa, normalization of left ventricular systolic blood pressure (L.V.SYS. PRESS.) is essentially due to a decrease in peripheral resistance (PERIPH. RESIST.). When compared with normal control animals, there remain significant hemodynamic abnormalities not fully compensated for by the action of methyldopa on arterial pressure. Values are means ± standard errors for 13 untreated spontaneously hypertensive rats, 36 treated spontaneously hypertensive rats and 10 normotensive control rats.

Effect of methyldopa on cardiac dynamics in spontaneously hypertensive rats: Measurements of hemodynamic variables in rats with established genetic hypertension both before and at the plateau of the ventricular function curves suggested moderate depression in the ability of the heart to eject blood. Thus, a separate group of 36 spontaneously hypertensive rats was given methyldopa for 3 or 6 weeks after which hemodynamic measurements were obtained both before and at the plateau of the ventricular function curve. Therapy with methyldopa produced normalization of arterial pressure and significant regression of cardiac hypertrophy (Table I).

The hypotensive effect of methyldopa was associated with a significant decrease in peripheral resistance to 94 ± 6 units compared with 145 ± 10 units ($P < 0.05$) in untreated spontaneously hypertensive rats. Treated animals displayed mild tachycardia[11] and a slight but statistically significant increase in cardiac output from the subnormal values measured in untreated animals (Fig. 2).

The effects of acute increases in cardiac inflow after methyldopa therapy are illustrated in Figure 4. In most instances, treated spontaneously hypertensive rats displayed values of peak cardiac output greater than those obtained in untreated animals. In the treated group as a whole, stroke volume and cardiac output at the plateau of the function curve averaged 0.41 ± 0.01

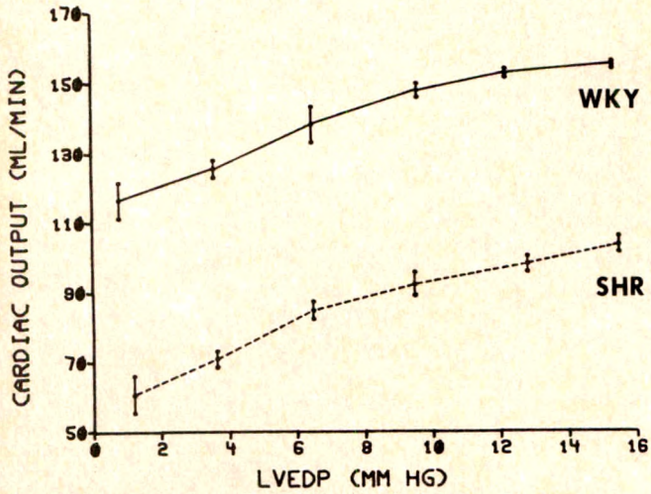

FIGURE 3. There is a remarkable difference in the cardiac pumping ability of rats with genetic spontaneous hypertension (SHR) compared with normotensive Wistar-Kyoto (WKY) control rats. At matched end-diastolic pressures, peak pumping ability is markedly depressed. Values are means ± standard error for 13 spontaneously hypertensive rats and 10 normotensive control rats averaged at 3 mm Hg increases in left ventricular end-diastolic pressure (LVEDP).

TABLE I

Effect of Methyldopa on Indirect Blood Pressure and Heart Weight of Spontaneously Hypertensive Rats (SHR)

Animals	Systolic Blood Pressure (mm Hg)	HW/BW (mg/g)	LV/BW (mg/g)
Untreated SHR	204 ± 2	3.64 ± 0.04	2.64 ± 0.03
Treated SHR	147 ± 3*	3.33 ± 0.03*	2.38 ± 0.03*

* Probability (P) <0.001.
Values are expressed as mean ± standard error of the mean.
BW = body weight; HW = heart weight; LV = left ventricular weight.

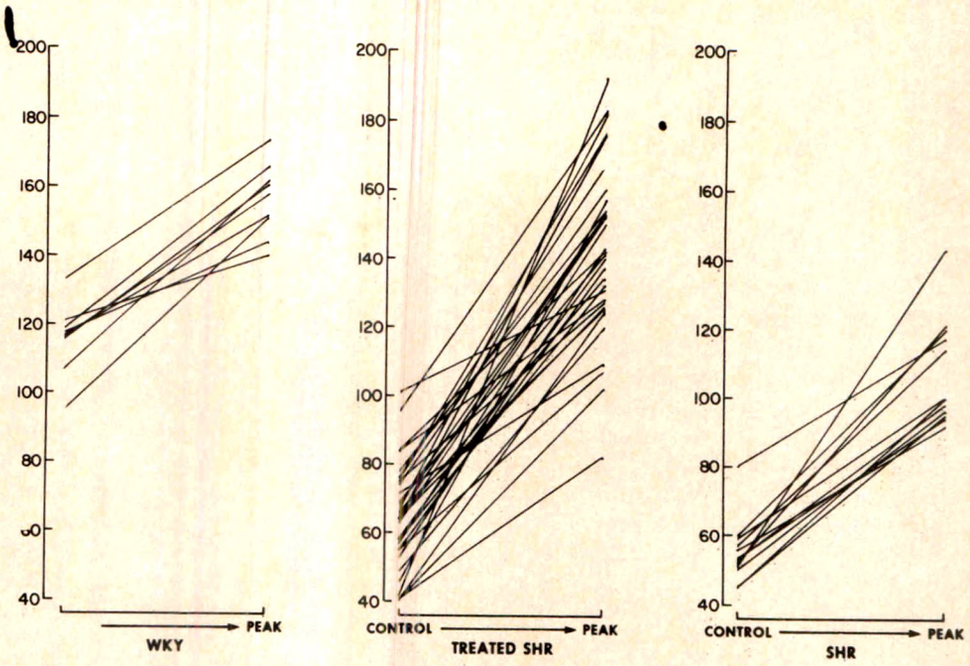

FIGURE 4. Cardiac output before (control) and at the plateau (peak) of the left ventricular function curve in normotensive Wistar-Kyoto (WKY) (**left panel**) treated (**middle panel**) and untreated (**right panel**) spontaneously hypertensive rats (SHR). On most occasions therapy with methyldopa produced a comparably larger increase in peak cardiac pumping ability suggestive of improved mechanical performance.

ml and 143 ± 3 ml/min respectively, compared with 0.35 ± 0.01 ml and 104 ± 2 ml/min in untreated spontaneously hypertensive rats. These differences were statistically significant ($P < 0.05$). In treated rats, peak stroke work was similar (77 ± 2 g·cm) to that obtained in untreated rats because the larger stroke volume compensated for the lower pressure.

Pressure load stress: Another experiment helped to clarify a reason for the improved pumping ability observed in spontaneously hypertensive rats treated with methyldopa. Taking into consideration that such therapy reduced arterial pressure, we wondered whether part of the increased performance was due to a reduction in the resistive load. Thus, a group of spontaneously hypertensive rats given methyldopa for 6 weeks were studied in terms of pumping ability at an arterial pressure now equivalent to that measured in untreated spontaneously hypertensive rats (Fig. 5). When cardiac pumping ability was determined with systolic pressure held at 148 ± 3 mm Hg instead of 135 ± 3 mm Hg, a pronounced depression in the previously improved ventricular performance amounting to −26 percent ($P < 0.001$) was noted in treated rats. At these hypertensive levels the peak cardiac output was not different from that recorded in untreated spontaneously hypertensive rats. Peak stroke work was depressed significantly (65 ± 1 in treated compared with 79 ± 1 in untreated spontaneously hypertensive rats and 99 ± 1 g·cm in normotensive control animals). In contrast, no further depression in pumping ability occurred as a result of a modest further increase in arterial pressure in untreated spontaneously hypertensive rats (from 153 ± 7 to 165 ± 4 mm Hg).

Discussion

Left ventricular dysfunction in hypertension: In both a renal (two kidney, one clip hypertension) and a genetic model of experimental hypertension, the established phase is accompanied by cardiac hypertrophy, normal[8] to subnormal[11] cardiac output and elevated total peripheral resistance. Left ventricular performance, estimated from the plateau of the ventricular function curves, was moderately reduced, raising a question regarding the role of myocardial restructuring in maintaining normal cardiac pumping ability. The data obtained in the present experiments are compatible with a previous suggestion by Spann et al.[16] that pressure-induced cardiac hypertrophy does not significantly alter a downhill course of myocardial depression leading to overt heart failure. Baseline left ventricular function judged in terms of cavitary pressures and

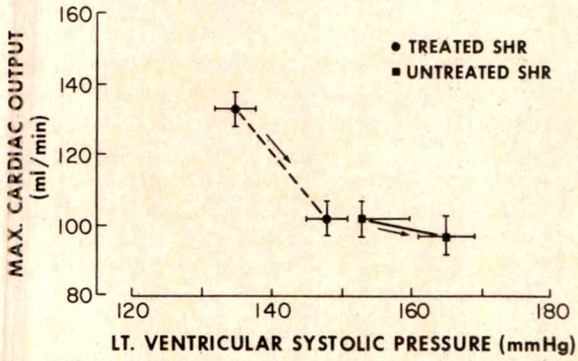

FIGURE 5. The influence of reduced arterial impedance on left ventricular ejection is manifested by the pronounced decline in pump performance after an infusion of phenylephrine in treated spontaneously hypertensive rats (SHR). Increasing the load against which the untreated ventricle pumps does not lead to further debilitation in mechanical performance. Values are means ± standard errors of the maximal (MAX.) cardiac output achieved during the preload stress as a function of the corresponding left (LT.) ventricular systolic pressure both before and after (**direction of arrow**) increasing peripheral resistance with phenylephrine.

cardiac output may be normal in hearts whose performance during more demanding stress reveals moderate degrees of functional impairment[17]; preload stress with rapid intravenous loading unmasked the occurrence of left ventricular dysfunction in the renal model[8] and confirmed its existence in the genetic model of hypertension.[11] Although there is no direct relation between left ventricular pumping ability and myocardial contractility, other investigators[7,12–14] have shown that a certain parallelism does exist. Braunwald et al.[17] have presented a comprehensive review of the problem.

Association of cardiac hypertrophy and left ventricular dysfunction: There are some reported discrepancies as to whether ventricular function may be depressed during the evolution of arterial hypertension accompanied by cardiac hypertrophy.[8,11,18,19] Increased performance suggestive of the stable hyperfunction of Meerson[20] was reported by Beznak[21] in rats with aortic constriction and by Pfeffer et al.[6,22] in young spontaneously hypertensive rats. With hypertension of longer duration (greater than 25 weeks), the spontaneously hypertensive rats studied by Pfeffer et al.[19] displayed reduced pumping ability despite further increases in cardiac weight. In hypertensive patients, various studies have shown, not unexpectedly, a wide spectrum of findings[23,24] probably because of the number of factors involved. The fact remains, however, that in the Framingham study hypertension was the primary antecedent of cardiac decompensation.

Role of cardiac output in hypertension: The effect of hypertension on cardiac pumping ability may also influence the sequence of hemodynamic events leading to the established phase of hypertension. The transition from a stage of high cardiac output to one of elevated peripheral resistance during the course of experimental hypertension has been attributed to whole body autoregulation.[5] Cardiac factors may also play a role. If we assume that the Frank-Starling relation is altered in the hypertrophied heart, the left ventricle may be unable to maintain normal cardiac output even in the presence of increased end-diastolic pressure and normalized wall stress. As indicated by Averill et al.,[8] depression of cardiac performance may thus become a limiting factor in the cardiovascular adjustment to sustained hypertension.[2] The data obtained in two models of chronic experimental hypertension are compatible with this view. Although in rats with renal hypertension the development of cardiac hypertrophy paralleled the increase in arterial pressure,[8,25,26] in spontaneously hypertensive rats cardiac hypertrophy may even precede the development of hypertension.[27] Therefore, in this genetic model, other factors may play an important role.

Limitations of preload stress test and ventricular function curves: A preload stress has frequently been used to assess the mechanical performance of the heart and to estimate cardiac reserve.[7,12–14] The term pumping ability was popularized by Bishop and Stone,[13] who also showed that in the dog ventricular function curves are adequate indexes of performance. The validity and limitations of this procedure in assessing pump performance when applied in small mammals such as the rat have previously been detailed.[8,21] Anesthesia, thoracotomy and artificial ventilation alter cardiovascular reactivity and reduce the gradient of pressure from peripheral to central veins. These factors account for a rightward shift of the function curve along the pressure axis and a reduction in both stroke volume and cardiac output.[12] The depressive effects of anesthesia and thoracotomy on blood pressure are much more marked in spontaneously hypertensive than in normal and renal hypertensive rats.[6,11] This is an obvious source of difficulty in evaluating studies because some investigators[28] tend to rely mainly on pressures obtained under light anesthesia and before thoracotomy. With preload stress, either blood[8] or Tyrode's solution[19] has been used to augment cardiac inflow. Blood is the desirable agent because acute hemodilution by the plasma expander (a) reduces arterial pressure during the study and (b) causes the electromagnetic flowmeter to overestimate cardiac output.[29] These factors might account for the greater peak cardiac output noted by Pfeffer et al.[19] in rats with spontaneous hypertension of about the same age as those we studied.[11] As reported elsewhere,[30] other factors including varied strains of rats, breeding conditions and laboratory protocol also limit comparison.

Effects of antihypertensive therapy: The hemodynamic effects of methyldopa observed in the present experiments are similar to those reported previously in man.[31–33] However, until now, no information was available on the changes in ventricular pumping ability after prolonged administration of methyldopa. This type of antihypertensive therapy both normalizes arterial pressure and reverses cardiac hypertrophy. A causal relation between these two factors does not necessarily exist because other drugs that also decrease blood pressure either have no effect or actually cause a further increase in cardiac weight.[34] In the present experiments, methyldopa had a beneficial effect on baseline levels of cardiac function and led to a remarkable improvement in pumping ability in terms of both peak stroke volume and cardiac output.

The improved performance with treatment was predominantly due to blood pressure control. When systolic blood pressure was increased acutely in spontaneously hypertensive rats treated with methyldopa, peak stroke volume and peak cardiac output decreased significantly (Fig. 5). In a previous study, Spech et al.[11] showed a moderate influence of blood pressure on the peak cardiac pumping ability of normotensive untreated Wistar-Kyoto rats. The comparably greater depression of pump performance observed in spontaneously hypertensive rats after an acute increase in the pressure load suggests a key influence of arterial pressure on pumping ability after reversal of cardiac hypertrophy.

The relation between pump function and outflow resistance or impedance varies with the condition of the heart.[35–37] In untreated spontaneously hypertensive rats a further but small increase in arterial pressure did not alter pump function, indicating that the hypertensive

hypertrophied heart can withstand an abrupt but moderate increase in blood pressure without further debilitating its performance. However, the marked reduction in peak stroke volume, cardiac output and stroke work that followed an acute increase in pressure in treated hypertensive rats poses a question on the state of pump performance or contractile properties, or both, of the myocardium after reversal of cardiac hypertrophy with methyldopa. Sen et al.[38] showed that reversal of cardiac hypertrophy with methyldopa led to increased hydroxyproline concentration in the myocardium. The influence of myocardial collagen on cardiac performance is still debated.[8,39,40] Possibly the smaller and presumably more fibrous heart of treated hypertensive rats is less able to cope with acute stresses that call for an increase in ventricular tension. More direct determinations of pressure-volume curves in treated animals are needed to evaluate the influence of increased hydroxyproline concentration in hearts with reversed hypertrophy.

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Hemodynamic Consequences of Left Ventricular Hypertrophy in Spontaneously Hypertensive Rats

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Compared with hearts from normotensive rats isolated, perfused hearts from spontaneously hypertensive rats exhibit a rightward shift of the Frank-Starling curve in the lower range of filling pressures, that is, up to 10 mm Hg. The extent of this shift is proportional to the degree of left ventricular hypertrophy. This is suggested to be a consequence of an altered relation between end-diastolic pressure and end-diastolic tension of the progressively more thick-walled left ventricle. Furthermore, the cardiac function curves revealed that maximal cardiac performance is apparently better in spontaneously hypertensive rats than in normotensive rats at increased levels of afterload. Therefore, left ventricular hypertrophy in established hypertension seems to contribute to adjustment of cardiac performance to the enhanced pressure work in hypertension; however, this occurs at the expense of a rightward shift of the Frank-Starling curve. In spontaneously hypertensive rats studied in vitro, coronary vascular resistance per unit weight of tissue was increased at maximal dilation, as was maximal pressor response. This may reflect the same type of structural vascular adaptation that occurs in most systemic vascular beds in hypertension and that contributes to maintenance of increased vascular reactivity and flow resistance in both hypertensive patients and spontaneously hypertensive rats. Apparently as a consequence of this adaptation, splanchnic nerve stimulation at an increasing rate caused exaggerated increases in resistance in anesthetized hypertensive rats by comparison with findings in normotensive rats. However, the effect of capacitance vessel constriction on stroke volume caused by splanchnic nerve stimulation was less pronounced in hypertensive rats. This relative "hyporeactivity" of the capacitance vessels also suggests an altered relation between cardiac filling pressure and stroke volume of the hypertrophied left ventricle in the spontaneously hypertensive rat.

One of the earliest findings in hypertension research was that of cardiac hypertrophy,[1] recognized long before the disease was clearly associated with an elevated mean arterial blood pressure. In the presence of increased blood pressure the tension within each myocardial fiber during systole increases, and this increase is thought to be the dominant stimulus for cardiac hypertrophy.[2] When the myocardial mass is increased, the stress per transverse sectional area of contractile element is normalized and a new balance between pressure load and myocardial mass is achieved.[3] Left ventricular hypertrophy in primary hypertension may thus be regarded as a "physiologic" adaptation whereby cardiac performance becomes matched to the chronically elevated pressure.

Cardiac performance is to a great extent determined by the filling of the heart through its impact on ventricular end-diastolic tension.[4] However, in the presence of concentric left ventricular hypertrophy, and hence an increased ventricular wall mass in relation to the end-diastolic radius, the tension per unit of wall thickness for a given end-diastolic

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pressure would be expected to be reduced.[2] Furthermore, left ventricular hypertrophy may also cause rearrangement of the myofibers, and this altered orientation may play a role altering the relation between end-diastolic pressure and end-diastolic tension.

The presence of such an altered relation was revealed in experiments where the pressure-volume-wall thickness relations of hypertrophied hearts from spontaneously hypertensive rats[5] were compared with these relations in hearts from normotensive control rats.[6] This altered relation is expected to result in a lower stroke volume for a given end-diastolic pressure in hypertrophied hearts than in normal hearts, and hence to lead to a rightward shift of the Frank-Starling curve. This rightward shift in the hypertrophied heart in hypertension has also been illustrated when isolated perfused hearts from spontaneously hypertensive rats were compared with those from matched normotensive rats.[6]

Frank-Starling Relation of Progressively More Hypertrophied Hearts

In Vitro Experiments

In a first set of experiments the stroke volume of hearts from 30 week old, that is, "adult" spontaneously hypertensive rats in the established phase of hypertension and of hearts from 6 week old spontaneously hypertensive rats, in the early "borderline" phase of hypertension, was compared with that of matched normotensive rats at varying end-diastolic filling pressures in vitro. Using an in vitro system instead of studying cardiac performance in vivo was considered a great advantage because all variables determining cardiac performance (cardiac preload, afterload, heart rate and the inotropic state of the heart) could be well controlled and also varied independently of each other.

The extirpated heart was placed in an anterograde perfusion apparatus and perfused with recirculating, continuously oxygenated Krebs-Henseleit bicarbonate buffer by way of the left atrium so that the heart was able to maintain its pumping function in vitro. The left ventricular filling pressure (preload) was determined by the level above the heart at which an atrial bubble trap was placed. Cardiac output was determined by collecting the aortic and coronary outflow. The perfusate entering the left atrium was pumped by the left ventricle to the top of an oxygenating chamber, 70 cm high. In this way the heart performed a mechanical work against a hydrostatic pressure that was determined by the height of the oxygenating chamber (50 to 55 mm Hg·mm Hg). In this first study "aortic" pressure was thus practically identical in hypertensive and normal rats while preload was altered in randomized fashion. A pressure transducer was connected to a side tube of the perfusion apparatus at the level of the heart, and aortic pressure and heart rate were recorded on a Sanborn recorder, model 16-1300S. The intrinsic heart rate remained constant throughout each experiment, which lasted for about 40 minutes.[6]

Established hypertension (Fig. 1, left): The influence of increasing diastolic filling pressure on stroke volume (that is, the Frank-Starling relation) was compared in the spontaneously beating hearts of 13 "adult" spontaneously hypertensive rats (blood pressure 164 ± 5 mm Hg [mean ± standard error]) and of 15 age-matched normotensive rats (blood pressure 119 ± 4 mm Hg). The hypertensive hearts had an 80 percent higher ratio of left ventricular dry weight to body weight than the normal hearts (0.68 ± 0.04 versus 0.37 ± 0.01 mg/g). In the lower "physiologic" range of diastolic filling pressures a definitely higher pressure was required for the hypertrophied left ventricle to produce the same stroke volume as that produced by the normal left ventricle, but there was no clear difference at high filling pressures. Thus, when the filling pressure was kept at 6 mm Hg for both spontaneously hypertensive and control rats the stroke volume in the former was 20 to

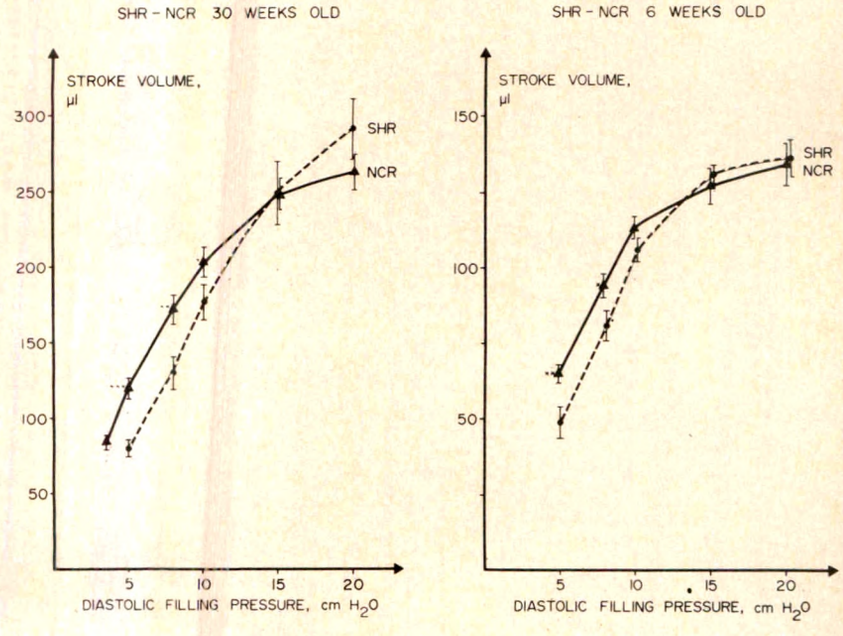

FIGURE 1. Left, relation between diastolic filling pressure and stroke volume (Frank-Starling relation) for 30 week old rats, 13 of the spontaneously hypertensive strain (SHR) and 15 normotensive rats working against an afterload of 50 mm Hg with a heart rate of 263 ± 20 and 280 ± 16 beats/min, respectively. **Right,** the same relation in ten 6 week old hypertensive and 8 normotensive rat hearts beating at a rate of 281 ± 20 and 308 ± 16 beats/min, respectively. The **vertical bars** indicate ± standard error. ** = probability (P) <0.001, *** = P <0.001. (Adapted from Hallbäck.[24])

25 percent lower than in the latter (130 ± 14 versus 172 ± 10 μliter).

Borderline hypertension (Fig. 1, right): Comparison was also made of the changes in stroke volume at increasing filling pressures in the left ventricle of 10 young (6 weeks) hypertensive rats (blood pressure 135 ± 6 mm Hg) and 8 age-matched normotensive rats (blood pressure 100 ± 3 mm Hg). These hypertensive rats had only a 40 percent increase in the ratio of left ventricular dry weight to body weight when compared with normal rats (0.66 ± 0.02 versus 0.48 ± 0.01 mg/g). Also there was a difference between these hypertensive and normal rats at equal diastolic filling pressures in the lower range, but this difference was less pronounced than that between the adult hypertensive and normal rats. Thus at a filling pressure of 6 mm Hg, stroke volume was only 10 to 13 percent lower in the hypertensive rat than in the normal rat (82 ± 5 and 94 ± 4 μliter, respectively).

It is clear from these data[6] that, with advancing hypertension and the progressively more pronounced left ventricular hypertrophy, the Frank-Starling relation in the hypertrophied left ventricle of the spontaneously hypertensive rat is almost proportionally "reset" toward the right in comparison with that in the normal ventricle, although stroke volumes are nearly equal when sufficiently high filling pressures are reached. Compensation for this rightward shift of the lower "physiologic" range of the Frank-Starling relation would require either an increased end-diastolic filling pressure for the hypertrophied ventricle or an increased inotropic stimulation, or both.

In Vivo Applications

When these findings are applied to the in vivo situation, where neurogenic influences are superimposed on the "heterometric autoregulation" of cardiac performance,[7] the maintenance of equal cardiac output in normal and spontaneously hypertensive rats with established hypertension suggests that the latter have a somewhat increased sympathetic drive to the capacitance side or to the heart or increased cardiovascular filling, or both. Several studies also indicate that sympathetic influence on the heart is increased in the spontaneously hypertensive rat.[5] The present findings of a progressive rightward shift of the Frank-Starling curve in hypertension and advancing left ventricular hypertrophy suggest that this increased sympathetic influence may produce in young spontaneously hypertensive rats an increase in stroke volume and cardiac output over normal values. This hemodynamic pattern often characterizes borderline hypertension in human beings.[8] For older spontaneously hypertensive rats, with more developed cardiac hypertrophy and reduced diastolic compliance, equally increased sympathetic discharge may help to ensure a largely normalized stroke volume and cardiac output which are generally found in established hypertension in human beings.

Cardiac performance in left ventricular hypertrophy: The extent of the rightward shift of the Frank-Starling relation appears to reflect directly the extent of left ventricular hypertrophy. We believe that this shift is due to the increased left ventricular wall thickness in spontaneously hypertensive rats, whereby as in our present experiments, the average tension per unit layer of cardiac muscle for a given pressure is less than that in a normal left ventricle. We therefore consider that the functional impact of increased filling pressure on stroke volume is reduced in hypertensive rats. However, it has been reported that left ventricular hypertrophy occurring after renal hypertension reduces cardiac performance, and that this reduction may reflect degenerative processes.[9,10] Thus, the rapidly developing hypertrophy of the individual myocardial cells after initiation of renal hypertension may alter their performance or, possibly, altered coronary flow distribution in a thick-walled ventricle may reduce its performance.

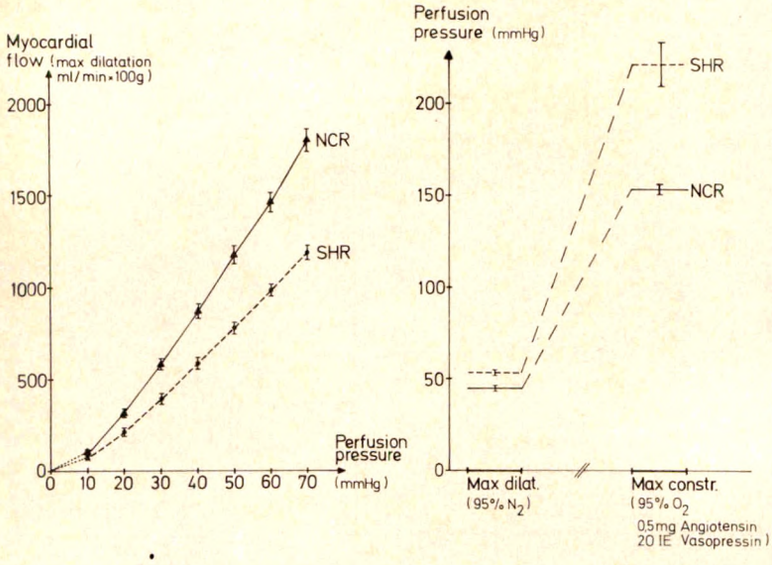

FIGURE 2. Left, relation between perfusion pressure and flow of the maximally dilated and artificially perfused coronary vascular bed of isolated hearts from 11 spontaneously hypertensive (SHR) and 11 normotensive control (NCR) rats. **Right,** perfusion pressure at constant flow (that is, resistance) at maximal coronary vasodilatation (max. dilat.) and maximal vasoconstriction induced by vasopressin and adenosine in the isolated hypertensive and normal hearts. The **vertical bars** indicate ± standard error. (Adapted from Noresson et al.[11])

In hypertensive rats reduced coronary flow for a given pressure and unit weight of tissue was, in fact, demonstrated when isolated hearts from normal and hypertensive rats were perfused during maximal vasodilatation in vitro.[11] However, this reduction was considered a reflection of the generalized structural vascular adaptation occurring in hypertension[12] rather than, in itself, a pathologic limitation of coronary flow reserve.

Coronary Flow Resistance

In a retrograde perfusion system the coronary vascular beds of isolated hearts from 11 "adult" spontaneously hypertensive rats and 11 age-matched normotensive rats were perfused with Krebs-Henseleit bicarbonate buffer while the perfusion pressure was continuously measured.[11] By means of a peristaltic pump, flow could be set at any level; thus, the resistance of the coronary vascular bed could be calculated at different levels of pressure and flow. Initially the perfusion medium was gassed with 5 percent carbon dioxide in oxygen and hence well oxygenated. During constant flow and at a steady pressure level, supramaximal amounts of vasopressin (20 IU) and angiotensin II (0.5 mg) were added to the 100 ml perfusate to estimate the maximal pressure response of the respective coronary vascular bed. The perfusate was then changed so that the pressure agents were eliminated. The new perfusate was gassed with 5 percent carbon dioxide in nitrogen instead of oxygen. This anoxic perfusion caused maximal coronary vasodilatation because no further reduction in resistance was seen after administration of adenosine (50 μmol). Flow was then altered in a random fashion so that the pressure-flow relation of the completely relaxed coronary vascular bed of the spontaneously hypertensive and normal rats could be compared.[11]

Coronary flow-pressure curve (Fig. 2): In Figure 2, left, the pressure-flow curve of the hypertensive rats is shifted to the right of that of the normotensive rats. Thus, at any given distending pressure the coronary resistance vessels of the hypertensive rat hearts exhibit a higher resistance per gram of myocardium than that of vessels in the normal rat hearts. This is also true during complete vascular relaxation. Further analysis of this pressure-flow curve reveals that coronary flow increments are relatively smaller for a given pressure increase in hypertensive than in normal rats, implying that the coronary resistance vessels of the former are less distensible than those of the latter. With the addition of supramaximal doses of vasopressin and angiotensin II (Fig. 2, right) the increase in coronary perfusion pressure was considerably greater in the hypertensive than in the normal control rats. Thus, the maximal perfusion pressure reached in the former was 221 ± 12 mm Hg versus 153 ± 3 mm Hg in the normal rat.

Altered coronary design in hypertension: When considered together these findings indicate that the coronary resistance vessels in the spontaneously hypertensive rat are rebuilt so that an increased media thickness encroaches on the vascular lumen even during maximal dilatation as well as during normal vascular tone. In a previous detailed hemodynamic study of hindquarter vascular beds in spontaneously hypertensive and normal rats, flow resistance at maximal dilatation in the normal rats was artificially raised, through graded microplugging of the hindquarter vessels to the resistance level in the hypertensive rats. However, this artificial elevation at complete vascular relaxation was not accompanied by any reduced vascular distensibility or increased maximal pressor response, which is regularly seen in the hindquarter,[13] coronary[11] and renal[25] vascular beds of spontaneously hypertensive rats. A reduced distensibility at maximal dilatation, particularly when combined with an increased contractile strength, strongly suggests the presence of thicker vascular walls with dominance for contractile tissue whereby the media thickness will be increased.[12,14] Therefore, the results presented in Figure 2—that is, an increased flow resistance at maximal dilatation and decreased vascular distensibility in combination with an increased maximal pressor response in spontaneously hypertensive rats—implies that the coronary resistance vessels exhibit the same type of adaptive structural change—"structural autoregulation"—as that of other systemic circuits in this rat strain.[12,15]

Myocardial effects: For the myocardium, one consequence is that at the *same* perfusion pressure, maximal coronary flow capacity per unit of tissue weight is lower in hypertensive than in normotensive subjects. The altered Frank-Starling relation of the isolated hearts in the spontaneously hypertensive rat might thus in part be due to a lower coronary perfusion in the experimental protocol in which the spontaneously hypertensive rat and normotensive rat hearts worked against similar aortic pressure. However, this explanation seems unlikely because the maximal stroke volume of the isolated spontaneously hypertensive rat hearts was equal to, or even somewhat higher than that of the normotensive rat hearts (Fig. 1, left).

The rightward shift of the Frank-Starling relation in spontaneously hypertensive rats might also be due to a progressive development of myocardial failure in association with left ventricular hypertrophy. If so, this rightward shift should be more pronounced at higher work loads. In contrast, if left ventricular hypertrophy in spontaneously hypertensive rats with established hypertension in essence constitutes a *physiologic* adaptation of myocardial tissue to increases in afterload, a *better* work performance would be expected of the isolated heart in these rats than of the heart of normal rats when afterload is increased. The Frank-Starling relation was therefore investigated in vitro in isolated perfused hearts from spontaneously hypertensive rats with considerable left ventricular hypertrophy and compared with that in hearts from age-matched normotensive rats while the left ventricles were working against *different* aortic pressures or afterloads.[16]

Effects of Increased Afterload on Cardiac Function

In this study the mean aortic pressure, defined as afterload, could be kept constant or set at any desired level by means of a modified Starling resistor, introduced on the arterial side of the perfusion system.[16] Left ventricular filling pressure (preload) could be altered

by changing the level of the atrial bubble trap above the heart, and the hearts were electrically paced to beat at a constant rate of 300 beats/min. Afterload, preload and heart rate were recorded by means of transducers connected to the perfusion system at the level of the heart and connected to a Grass Polygraph. The Frank-Starling relation in 17 "adult" spontaneously hypertensive rat hearts with a 35 percent increase in left ventricular wet weight per unit body weight, and of 17 age-matched normotensive hearts were thus compared at five different levels of constant afterload ranging from 50 to 150 mm Hg (Fig. 3).[16]

Effect of afterload on stroke volume: When compared at low levels of afterload (50 and 80 mm Hg) stroke volume per unit body weight was lower in hypertensive than in normal control rats at equal filling pressures up to 10 to 12 mm Hg. The highest stroke volume obtained during these experimental conditions was 77 +3 μliter/100 g body weight in normal rats and 82 ± 2 in hypertensive rats; in both strains this occurred at an afterload of 80 mm Hg, although the hypertensive rats needed a higher preload than the normal rats to reach this maximum (15 versus 10 mm Hg).

At higher levels of afterload stroke volume was more reduced in normal than in spontaneously hypertensive rats for any given level of diastolic filling pressure (Fig. 3). Thus an increase in afterload from 80 mm Hg (arbitrarily set to represent "normotension") to 130 mm Hg (representing "hypertension") reduced maximal stroke volume by 30 percent in normal rats but only by 11 percent in hypertensive rats. These differences became even more pronounced when afterloads of 80 and 150 mm Hg were compared (Fig. 3). Furthermore, at afterloads of 130 and 150 mm Hg the cardiac function curves of the hypertensive rats were much steeper than those of the normal rats, indicating that the normal left ventricle was then working close to its maximal performance already at lower filling pressures (Fig. 3). In contrast, the hypertensive left ventricle has at these high levels of afterload a far better capacity to regulate its work performance by alterations in preload. These findings therefore indicate that the hypertrophied spontaneously hypertensive rat heart can produce a better external work at high levels of afterload than can the heart of the normal rat, at least in early established hypertension.

Stroke volume and cardiac output in the hypertrophic heart: In vivo the heart of the spontaneously hypertensive rat works against a higher afterload than the normotensive heart. This situation is mimicked if the Frank-Starling relations obtained in vitro in the normotensive heart at an afterload of 80 mm Hg are compared with those obtained in the hypertensive heart at 130 mm Hg, since this difference in afterload levels largely reflects that present in vivo. Figure 4 shows that the Frank-Starling curve of the hypertensive rats is

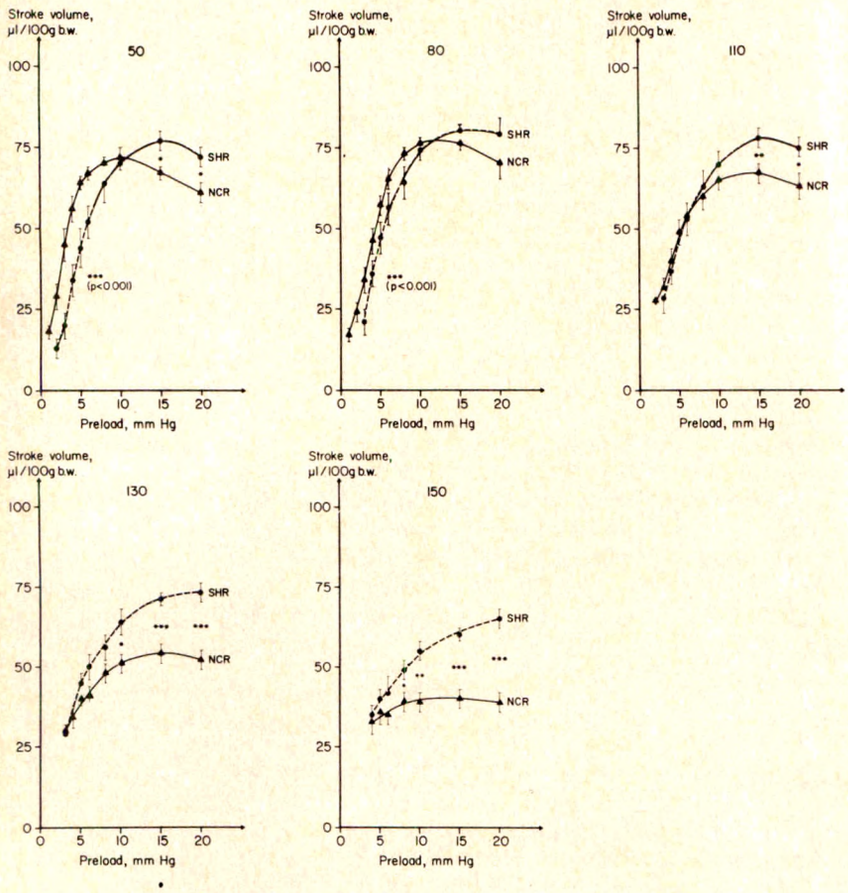

FIGURE 3. Relation between left ventricular filling pressure, that is, preload, and stroke volume per 100 g body weight (b.w.) of isolated hearts from spontaneously hypertensive (SHR) and matched normotensive (NCR) rats studied in an anterograde perfusion system at five different levels of afterload, ranging from 50 to 150 mm Hg. The **vertical bars** indicate standard error. * = probability (P) <0.05, ** = $P<0.01$, *** = $P<0.001$. (Adapted from Noresson et al.[16])

clearly displaced to the right of the curve of the normal rats. Also, the curve of the normotensive rats obtained at an afterload of 130 mm Hg indicates how a nonhypertrophied heart works at a hypertensive level. The curve of the spontaneously hypertensive rats is displaced to the left of this latter curve, and reaches a definitely higher maximal stroke volume. This figure thus suggests that the hypertrophied left ventricle of the hypertensive rat can better maintain an adequate stroke volume at increased arterial pressures than would have been possible without such structural myocardial adaptation. However, when the cardiac function curves of normal and hypertensive rats are thus compared, the stroke volume at equal levels of preload is smaller in hypertensive rats than in normotensive rats. Extrapolated to the in vivo situation these findings may imply that stroke volume, and hence cardiac output, would tend to decrease in association with the progression of hypertension and concomitant left ventricular hypertrophy if no compensatory adjustments occur. Several clinical[17] and experimental[18] studies of essential hypertension also point in this direction. However, the present results were obtained in hearts from spontaneously hypertensive rats in a phase of established hypertension, in which stroke volume was still largely the same as in age-matched normotensive rats in vivo.[18,19] Therefore, some compensation for the altered Frank-Starling relation is evident in the intact spontaneously hypertensive rat, in the form of an increased left ventricular filling pressure or an increased inotropic stimulation to the heart, or both.

In vivo measurements of left atrial pressure in adult spontaneously hypertensive rats and age-matched normotensive rats revealed a considerable difference. Thus, in the awake, resting animals 1 week after implantation of a catheter in the left atrium,[20] left atrial pressure was twice as great in hypertensive as in normotensive rats (10 versus 5 mm Hg). This enhanced cardiac filling pressure may be at least partly responsible for the maintenance of equal stroke volume in spontaneously hypertensive and normal rats despite the rightward shift of the Frank-Starling curve in the former. Because circulating blood volume is not increased in spontaneously hypertensive rats,[21] it may be that the entire low pressure compartments of the circulation, with their important capacitance function in relation to left ventricular filling, somehow becomes adjusted to balance the reduced left ventricular diastolic compliance in the hypertensive rat. This adjustment of the low pressure compartments may be the result of increased neurogenic influence on, or a structurally reduced compliance of, the capacitance sections, or both, thus permitting cardiac filling pressure to be kept enhanced. Direct recordings of sympathetic activity specifically to the venous side of the circulation are difficult to perform. However, both in anesthetized[5] and awake[22] spontaneously hypertensive rats an increased sympathetic discharge rate has been recorded in the splanchnic area, which contains a particularly voluminous capacitance section. Interferences with the nervous control of this particular vascular bed might therefore reveal if spontaneously hypertensive differ from normotensive rats in stroke volume changes caused by changes in the neurogenic control of capacitance vessels.

Structural Cardiovascular Adaptations and Neurogenic Control of Resistance and Capacitance Functions

Cardiovascular "reactivity" to graded splanchnic nerve stimulation: Cardiovascular reactivity was compared in anesthetized adult spontaneously hypertensive and normal rats while adrenal medulla secretion, neurogenic cardiac control and major reflex vascular adjustments were abolished. Heart rate, blood pressure and cardiac output (the latter assessed with a dye-dilution technique in microscale) were measured and total peripheral resistance and stroke volume computed, before, during and after graded vasoconstrictor fiber stimulations.[23] The splanchnic vascular bed was thus chosen because it exhibits considerable capacitance as well as resistance functions within the gastrointestinal, liver and kidney circuits. Alterations in vasoconstrictor fiber influence will here affect both the resistance vessels, often mentioned major circuits, which causes corresponding changes in total peripheral resistance, and the voluminous splanchnic capacitance vessels thereby causing changes in cardiac filling and hence in stroke volume.

Upon splanchnic nerve section cardiac output was reduced 20 percent more in spontaneously hypertensive than in normal rats. This finding suggests that the hypertrophied heart of these hypertensive rats is dependent on an intact capacitance vessel innervation so that an adequate cardiac filling pressure is maintained. The effects of splanchnic nerve stimulation at increasing frequencies on stroke volume, blood pressure and total peripheral resistance of 14 spontaneously hypertensive rats (blood pressure 169 ± 4 mm Hg) and of 14 matched nor-

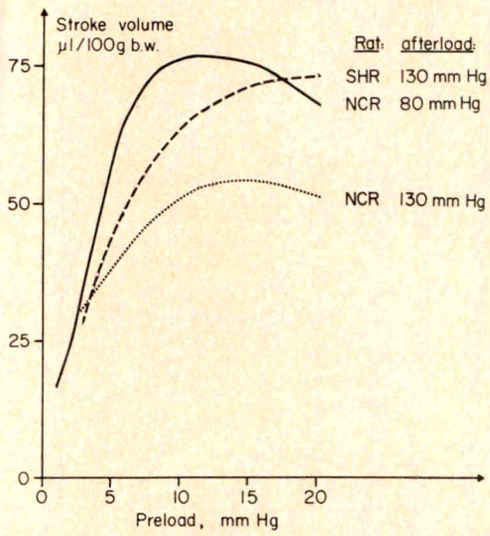

FIGURE 4. Relation between preload and stroke volume per 100 g body weight (b.w.) in isolated spontaneously hypertensive rat (SHR) hearts working against an afterload of 130 mm Hg and hearts of normotensive rats (NCR) working against afterload levels of 80 and 130 mm Hg. The curves are taken from Figure 3.

mal rats (blood pressure 111 ± 4 mm Hg) are shown in Figure 5. The right panel shows that the increases in neurogenic resistance were greater, both relatively and absolutely, in spontaneously hypertensive than in normal rats despite a higher distending pressure in the former. Whereas total peripheral resistance in normal rats increased maximally by 32 percent from an initial value of 10.2 peripheral resistance units/100 g, in hypertensive rats it increased by 70 percent from an initial value of 15.2 peripheral resistance units/100 g. Thus, even in relative terms, the increase in total peripheral resistance on constrictor fiber stimulation was twice as great in hypertensive as in normal rats. Further, the curve relating stimulation frequency to changes in total peripheral resistance was clearly steeper in hypertensive rats, reaching 50 percent of the maximal increase in resistance at a lower frequency than in normal rats. Stroke volume was initially about 10 percent higher in normal than in hypertensive rats and it also increased more steeply in the normal group at low rates of splanchnic nerve stimulation (Fig. 5, left). Thus, half of the maximal increase in stroke volume (26 percent) induced in normal rats by splanchnic vasoconstrictor fiber stimulation was reached at 1.4 hertz; the corresponding figures for hypertensive rats were 19 percent and 2.8 hertz. The neurogenic increase in blood pressure (Fig. 5, center) is the product of the increases in cardiac output and total peripheral resistance. The absolute increase in blood pressure on maximal splanchnic nerve stimulation was 77 mm Hg (70 percent) for hypertensive rats and 49 mm Hg (60 percent) for normotensive rats. In both rat groups, to restore the blood pressure level present after the abdominal opening when the sympathetic control of the splanchnic vessels was still intact (137 and 114 mm Hg, respectively) largely the *same* rates of splanchnic nerve stimulation, about 2 hertz, were needed. However, this discharge rate caused a larger increase in stroke volume in the normal rats, whereas the increase in total peripheral resistance was correspondingly more pronounced in the hypertensive rats.[23]

Neurogenic control of resistance and capacitance function in hypertension: This study thus illustrates that graded stimulations of the vasoconstrictor fibers to the major splanchnic vascular circuits in spontaneously hypertensive normal rats, and through a hemodynamic impact on cardiac filling pressure, produced less pronounced increases in stroke volume in the former than in the latter. This relative "hyporeactivity" concerning changes in stroke volume caused by "capacitance vessel" responses in hypertensive rats is suggested to reflect predominantly the lower diastolic compliance and hence altered Frank-Starling relation of the hypertrophied left ventricle of these rats. In contrast, the splanchnic *resistance* vessels of these rats displayed a "hyperreactivity" with respect to graded vasomotor nerve stimulation, evidently due to the altered vascular structure. Thus, the cardiovascular system in hypertension may have increasing difficulty in modulating the neurogenic control of the resistance and capacitance function because the structural adaptations of heart and resistance vessels tend to cause a relatively reduced cardiac output and a disproportionately enhanced total peripheral resistance at a raised level of blood pressure. To normalize such a situation by way of neurogenic control it would be necessary to reduce sympathetic discharge to the resistance vessels and to enhance it to the capacitance vessels, and these differentiated adjustments are probably beyond the capacity of bulbar cardiovascular centers.

Conclusion

The studies reported here indicate that in the spontaneously hypertensive rat heart, as hypertension develops, the Frank-Starling relation of the progressively more hypertrophied heart becomes displaced to the right of that in the normotensive control heart. We suggest that this shift of the Frank-Starling curve, the extent of which is largely proportional to the degree of left ventricular hypertrophy, is a consequence of an altered relation between end-diastolic *pressure* and end-diastolic *tension* in thick-walled ventricle. The hypertrophy also implies that the left ventricle copes

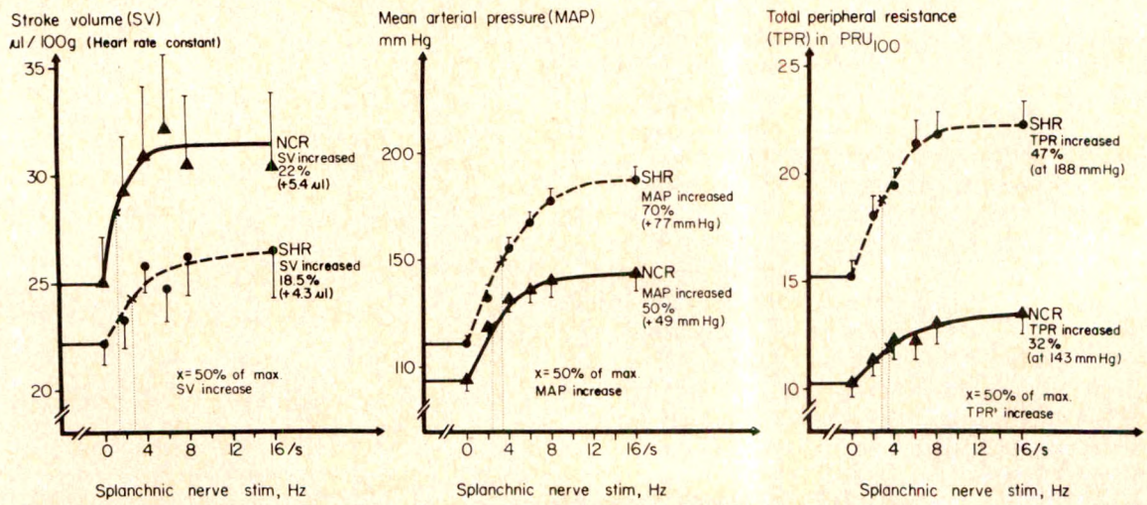

FIGURE 5. Relation between splanchnic nerve stimulation at increasing frequencies and stroke volume (**left**), mean arterial pressure (**center**) and total peripheral resistance, expressed as mm Hg/ml × 100 g tissue (**right**), in 17 spontaneously hypertensive (SHR) and normotensive (NCR) rats in which adrenal medullary secretion, neurogenic cardiac control and reflex vascular adjustments are largely abolished. The **vertical bars** indicate ± standard error. (Adapted from Noresson et al.[23])

more efficiently with increases in afterload, provided that the diastolic prestretch is adequate. However, if no adequate compensation occurs in the form of increased filling pressure or increased inotropic influence to the heart, or both, stroke volume would tend to be reduced in association with the progression of hypertension and the consequent left ventricular hypertrophy. Perhaps this explains why stroke volume and cardiac output tend to become normalized or even reduced in established hypertension, after having been modestly raised in early more or less hyperkinetic phases when sympathetic activity to the heart often seems to be increased.[8,17,24,25] Thus, because of the progressive structural adaptation of left heart and resistance vessels the hyperkinetic circulatory state frequently characterizing early primary hypertension[17] may gradually be converted into that of "established" hypertension with a basically normal cardiac output but an increased total peripheral resistance.

Acknowledgment

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Alterations of Cardiac Performance in Rats With Established Spontaneous Hypertension

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To characterize intact cardiac performance during the progression from moderate to severe left ventricular hypertrophy, peak pumping ability, maximal pressure-generating capacity and passive pressure-volume relations were determined in ether-anesthetized 6 and 18 month old female spontaneously hypertensive rats, in 18 month old male spontaneously hypertensive rats and in sex- and age-matched normotensive rats. Ejection phase indexes of young female hypertensive rats were comparable with those of age-matched normotensive rats. Both groups ejected the same peak stroke volumes from similar end-diastolic volumes so that their indexes of ejection fraction were identical. However, in old female and male hypertensive rats, these characteristics of ventricular performance were greatly diminished. A reduced peak stroke volume was ejected from a normal end-diastolic volume in old female hypertensive rats and from a significantly larger end-diastolic volume in old male hypertensive rats, so that ejection fraction indexes were moderately and substantially reduced, respectively. Maximal pressure developed during an aortic occlusion was always significantly greater in hypertensive rats. Despite elevated systemic arterial blood pressures, young female hypertensive rats ejected a normal stroke volume from a normal end-diastolic volume. Even though the severity of hypertension did not further progress with age, cardiac mass increased, yet systolic function decreased in old hypertensive rats. Therefore, hypertrophic growth of the left ventricle in the hypertensive rat is associated with both a compensated and a depressed phase of cardiac performance.

In organ systems other than the heart, hypertrophic growth is generally viewed as a process that extends functional capacity. Cardiac hypertrophy, however, is often associated with cardiac failure and decompensation. In cardiovascular diseases the increased functional demands imposed on the heart are often progressive and organ failure ensues despite rather than because of hypertrophy.

In our previous studies of young and mature spontaneously hypertensive rats, we noted normal blood flow and reserve capacity in the presence of marked systemic hypertension.[1,2] However, with advanced age and continued hypertrophic growth, left ventricular functional capacity was not maintained. Although the blood pressures of 12, 24, and 83 week old hypertensive rats were similar, only the oldest group had reduced pumping ability. Therefore, in this animal model of genetic hypertension, we have found both a compensated and a depressed phase of cardiac performance: in young rats with moderate left ventricular hypertrophy the peak pumping ability was normal whereas in old rats with long-standing hypertension and marked hypertrophy, decompensation occurred and pumping ability was severely reduced.

In the present study, our objective was to characterize more fully the performance of the intact left ventricle in situ in terms of peak pumping ability, maximal pressure-generating capacity and passive pressure-volume relations during the progression from moderate to severe left

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ventricular hypertrophy in the spontaneously hypertensive rat.

Methods

Material: Experiments were performed on two strains of normotensive rats, the Wistar-Kyoto (WKY) and an American Wistar (NWR), and on spontaneously hypertensive rats (SHR). Female rats were studied at 6 months (7 SHR, 7 WKY) and at 18 months (8 SHR, 4 WKY, 2 NWR) of age. Male rats were also studied at 18 months (7 SHR, 3 WKY, 7 NWR). All rats were obtained from our colony of inbred (brother to sister) spontaneously hypertensive and Wistar-Kyoto normotensive rats and randomly bred American Wistar normotensive rats.

Experimental procedures and recordings: The surgical preparation has been described in detail previously[3,4] and is presented here in brief. Under ether anesthesia, a catheter was advanced by way of the right carotid artery into the left ventricle for measurements of systolic and end-diastolic pressures and first derivative of pressure (dP/dt) and then withdrawn into the aorta for measurements of phasic and mean arterial pressures. A second catheter was inserted into the right jugular vein and advanced to the right atrium for continuous measurement of right atrial pressure. The rat was then ventilated by a positive pressure respirator connected in series to an ether drip apparatus. The chest was opened, and an electromagnetic flow probe placed around the ascending aorta permitted measurements of blood flow (less coronary flow) and its first derivative, the acceleration of aortic blood flow. Phasic and mean pressures and flow were recorded at 2 minute intervals over a stable 10 minute period to determine the baseline values for each rat.

Tyrode solution (40 ml/min per kg) was then infused for 45 seconds into a femoral vein, producing a prompt rise in cardiac output to a plateau; at this point the continued infusion further elevated venous pressure yet failed to increase blood flow.[1] The maximal cardiac output and stroke volume attained served as indexes of the peak pumping ability of the intact left ventricle.

All hemodynamic variables returned to baseline levels within 15 minutes. The flow probe was removed and the arterial catheter advanced into the left ventricle for continuous monitoring of intraventricular pressure and its first derivative, dP/dt. End-diastolic pressure was displayed at a high sensitivity on an additional channel. The ascending aorta was then occluded briefly with a suture to produce isovolumic (except for coronary flow) contractions. Developed pressure (peak systolic minus end-diastolic) was calculated from measurements of peak left ventricular systolic and end-diastolic pressures obtained during the first 7 beats of aortic occlusion.

After diastolic arrest of the heart with intravenous potassium chloride, a double lumen catheter was inserted into the left ventricular cavity by way of the aorta and secured into place with a suture around the atrioventricular groove. Three repeatable pressure-volume curves, obtained within 10 minutes of arrest and before the onset of rigor mortis, were determined with saline solution infused at a rate of 0.68 ml/min over a pressure range of −5 to 30 mm Hg.

The information on ventricular volumes and peak stroke volumes was combined to derive an index of ejection fraction as follows: In separate groups of normotensive and hypertensive rats it was determined that the volume-loading procedure with Tyrode solution which was carried out in vivo as described earlier increases left ventricular end-diastolic pressure to 17 to 20 mm Hg. This pressure range corresponds to a very steep portion of the pressure-volume curve determined in vitro so that volume changes per millimeter of mercury within that range are minimal. The ejection fraction index was then obtained by dividing the peak stroke volume of each rat determined during volume loading in vivo by the ventricular volume at 20 mm Hg from that rat's pressure-volume curve determined in vitro.

Statistical analysis: Because no differences were found between Wistar-Kyoto and American Wistar rats, the data from these two normotensive groups were pooled for comparison with age-matched spontaneously hypertensive rats. For all variables except peak stroke volume (for which male and female rats were analyzed separately), a one-way analysis of variance of the six groups of rats was performed. When the difference between groups was significant (Fisher's F ratio), the pooled error mean square was used to test the significance of the mean difference of the three planned comparisons between age- and sex-matched hypertensive and normotensive rats (Student's unpaired t test).[5] Data are expressed as the mean (± standard error of the mean) within a group.

Results

Left ventricular weight (Table I): Left ventricular weight in 6 month old female hypertensive rats was significantly increased by 25 percent compared with that of age-matched female normotensive rats of similar body weight. By age 18 months the amount of left ventricular hypertropy had more than doubled in both female (+64 percent) and male (+55 percent) hypertensive rats, although arterial pressures did not further increase (Table II). Despite the marked left ventricular hypertropy of old female hypertensive rats, right ventricular weights remained normal when expressed either as absolute values or in relation to body weight. In old male hypertensive rats, right ventricular weights were significantly increased.

TABLE I

Body and Ventricular Weights of Normotensive (Norm) and Spontaneously Hypertensive Rats (SHR)

	Female Rats				Male Rats	
	6 Months		18 Months		18 Months	
	Norm (no. = 7)	SHR (no. = 7)	Norm (no. = 6)	SHR (no. = 8)	Norm (no. = 10)	SHR (no. = 7)
Body weight (g)	238 ± 5	230 ± 3	255 ± 7	254 ± 4	424 ± 17	468 ± 21
Left ventricular weight (mg)	538 ± 19	677 ± 14†	623 ± 35	1022 + 35†	924 ± 53	1431 ± 68†
Left ventricular weight/body weight (mg/g)	2.24 ± 0.04	2.94 ± 0.06†	2.45 ± 0.06	4.03 ± 0.13†	2.06 ± 0.06	3.39 ± 0.10†
Right ventricular weight (mg)	146 ± 9	163 ± 9	173 ± 12	193 ± 8	267 ± 12	330 ± 21*
Right ventricular weight/body weight (mg/g)	0.61 ± 0.02	0.70 ± 0.04	0.67 ± 0.06	0.78 ± 0.03	0.62 ± 0.03	0.79 ± 0.06*

* $P < 0.01$, † $P < 0.001$ (spontaneously hypertensive versus age-matched normotensive rats).

TABLE II

Prethoracotomy Hemodynamic Characteristics of Normotensive (Norm) and Spontaneously Hypertensive Rats (SHR)

	Female Rats				Male Rats	
	6 months		18 months		18 Months	
	Norm	SHR	Norm	SHR	Norm	SHR
Arterial pressures (mm Hg)						
Systolic	139 ± 4	173 ± 1†	140 ± 4	176 ± 14*	137 ± 4	181 ± 17*
Mean	120 ± 4	149 ± 2‡	119 ± 4	145 ± 10*	119 ± 4	158 ± 14*
Diastolic	99 ± 4	125 ± 2‡	98 ± 4	123 ± 9*	101 ± 3	134 ± 14*
Left ventricular end-diastolic pressure (mm Hg)	3.6 ± 0.5	3.7 ± 0.5	4.2 ± 0.5	3.8 ± 0.3	3.9 ± 0.5	5.7 ± 0.5*
+dP/dt (mm Hg/sec)	18,165 ± 1239	20,122 ± 732	17,074 ± 1494	15,976 ± 1152	17,074 ± 1494	16,009 ± 1034
−dP/dt	11,082 ± 787	14,638 ± 570†	11,405 ± 1143	9,398 ± 844	10,607 ± 650	10,033 ± 1379
Mean right atrial pressure (mm Hg)	−0.2 ± 0.5	−0.2 ± 0.2	0.4 ± 0.4	0.1 ± 0.8	0.3 ± 0.4	1.7 ± 1.1
Heart rate (beats/min)	428 ± 8	424 ± 7	419 ± 15	411 ± 11	407 ± 7	406 ± 10

* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$ (spontaneously hypertensive versus age-matched normotensive rats).

Pressures (Table II): Arterial blood pressures of all groups of hypertensive rats were significantly higher than normal. There were no differences in heart rate or mean right atrial pressure between normotensive and hypertensive rats for any group examined. Left ventricular end-diastolic pressures were normal in both young and old female hypertensive rats, but were moderately, although significantly, increased in 18 month old male hypertensive rats. Despite differences in arterial blood pressures, no differences in maximal positive or negative dP/dt occurred, except in young female hypertensive rats with a greater negative dP/dt.

Stroke volume, ejection fraction and acceleration of aortic flow (Table III): The peak stroke volume, ejection fraction index and maximal acceleration of aortic blood flow during volume loading were normal in 6 month old female hypertensive rats when compared with age-matched normotensive rats. In contrast, these indexes were significantly reduced in both 18 month old female and male hypertensive rats. Despite an increase in body weight and a marked increase in ventricular mass, peak stroke volume was significantly decreased. In 18 month old female hypertensive rats, this reduced stroke volume was delivered from a normal end-diastolic volume so that ejection fraction index was only moderately reduced. However, in old male hypertensive rats a reduced peak stroke volume was ejected from a ventricle that was significantly dilated at the high distending pressures that occurred during volume loading, so that the ejection fraction index was substantially reduced. Similarly, maximal acceleration of aortic blood flow was significantly decreased in 18 month old female hypertensive rats and even more so in 18 month old male hypertensive rats. Maximal developed pressure was significantly greater in every hypertensive group.

Discussion

Ventricular hypertrophy is a principal mechanism by which the heart responds to a sustained imposition of an augmented load. In pressure overload hypertrophy the increased wall thickness reduces wall tension[6] and permits the ejection of a normal stroke volume against the increased resistance. However, with a pressure load of long-standing duration, impaired ventricular pumping performance may occur despite increases in cardiac mass. In our previous study of peak pumping ability of three age groups of male spontaneously hypertensive rats, the peak stroke volume and cardiac output of 11 and 24 week old hypertensive rats were comparable with values for age-matched normotensive rats despite the elevated arterial pressure of the former group.[1] However, at these same elevated pressure levels, 19 month old hypertensive rats were unable to eject the same stroke and minute volumes ejected by young hypertensive rats and age-matched normotensive rats.[1]

Cardiac performance in young versus old hypertensive rats: In the present study, an impairment of cardiac pumping ability also was demonstrated in 18 month old hypertensive rats. An altered ventricular compliance could explain the reduction in stroke volume; that is, there could be a reduction in ventricular volume at any given end-diastolic pressure in the hypertensive rats. Averill et al.[7] found that renal hypertensive rats had less stroke volume and cardiac output at left ventricular end-diastolic pressures greater than 10 mm Hg than did their normotensive counterparts. They found a twofold increase in hydroxyproline content in the hearts of the hypertensive rats and suggested that a decreased ventricular compliance might account for the reduced stroke volume. Hallbäck et al.[8] demonstrated a reduced stroke volume at normal ventricular diastolic pressures in an isolated working heart preparation when spontaneously hypertensive rats were compared with normotensive rats at 6 and 30 weeks of age. However, the passive pressure-volume relations determined in our study do not show a decreased compliance in either 6 or 18 month old hypertensive rats, as evidenced by the volumes measured at 5, 10 and 20 mm Hg. In fact, the volumes at 10 and 20 mm Hg in the 18 month old male hypertensive rats were significantly

TABLE III

Peak Pumping Ability of Normotensive (Norm) and Spontaneously Hypertensive Rats (SHR)

	Female Rats				Male Rats	
	6 Months		18 Months		18 Months	
	Norm	SHR	Norm	SHR	Norm	SHR
Peak stroke volume (ml)	0.30 ± 0.01	0.31 ± 0.11	0.35 ± 0.02	0.30 ± 0.02*	0.50 ± 0.03	0.35 ± 0.01†
End-diastolic volume (ml) at:						
5 mm Hg	0.26 ± 0.01	0.26 ± 0.02	0.31 ± 0.02	0.30 ± 0.02	0.39 ± 0.02	0.48 ± 0.05
10 mm Hg	0.34 ± 0.01	0.34 ± 0.02	0.41 ± 0.02	0.41 ± 0.02	0.55 ± 0.02	0.66 ± 0.04*
20 mm Hg	0.40 ± 0.01	0.41 ± 0.02	0.48 ± 0.02	0.50 ± 0.02	0.69 ± 0.02	0.80 ± 0.04*
Ejection fraction index (%)	76 ± 3	76 ± 3	75 ± 7	61 ± 3*	73 ± 4	44 ± 2‡
Maximal acceleration of aortic blood flow (g)	21.8 ± 0.4	20.7 ± 1.7	17.9 ± 1.6	14.1 ± 0.7*	19.4 ± 0.7	12.7 ± 0.9‡
Peak developed pressure (mm Hg)	222 ± 4	273 ± 4‡	215 ± 8	291 ± 9‡	212 ± 4	260 ± 23‡

* $P < 0.05$, † $P < 0.01$, ‡ $P < 0.001$ (spontaneously hypertensive versus age-matched normotensive rats).

greater than those of age-matched normotensive rats. However, passive pressure-volume relations determined in vitro may not be representative of compliance characteristics existing in vivo and it is possible that incomplete ventricular relaxation may reduce ventricular compliance. Nonetheless, we measured negative dP/dt as an indicator of ventricular relaxation and found that it was not reduced in any group of hypertensive rats.

The ratio of the peak stroke volume ejected from the maximal end-diastolic volume attained during volume loading is presented as an index of ejection fraction. Although impaired in 18 month old male and female hypertensive rats, this index was normal in 6 month old female hypertensive rats. This reduced index of ejection fraction was not related to an increase in blood pressure, because arterial pressures did not increase between 6 and 18 months in our hypertensive rats.

Cardiac performance in hypertensive patients. In human beings, both a compensated and a decompensated phase of cardiac performance has been found. Strauer[9] has shown in cardiac catheterization studies that patients with essential hypertension and left ventricular hypertrophy without coronary artery disease demonstrate normal ventricular function at rest and during exercise. Using echocardiographic techniques, Karliner et al.[10] found normal end-diastolic diameters and ejection fraction in patients with systemic arterial hypertension and left ventricular hypertrophy, without clinical evidence of coronary artery disease. In a much larger group of patients (234 hypertensive and 124 normotensive subjects), Savage et al.[11] also found ejection fraction and end-diastolic transverse diameters to be within normal limits in hypertensive subjects with mild to moderate hypertension and left ventricular hypertrophy. A decrease in ejection fraction was found by Toshima et al.[12] only in hypertensive patients considered to have congestive heart failure. Other echocardiographic studies[13,14] have shown a decrease in ejection fraction with an increase in the severity of hypertension.

Mechanisms of impaired performance of the hypertrophic left ventricle: The reduced ejection of blood from a normal end-diastolic volume suggests that impaired cardiac performance in the spontaneously hypertensive rat is not a result of inadequate filling but a consequence of systolic dysfunction. The rate of change of aortic flow velocity, or maximal acceleration of aortic blood flow, has been shown to be a valid index of the initial phase of ventricular ejection.[15,16] When measured during volume loading, to eliminate possible differences in preload, maximal acceleration of aortic blood flow was significantly decreased in old female and male hypertensive rats with reduced indexes of ejection fraction, yet was normal in young female hypertensive rats whose index of ejection fraction was comparable with that of normotensive rats.

In spontaneously hypertensive rats, the hypertrophic response of the left ventricle to a pressure load initially permits a normal ejection of blood flow. With increasing duration of this afterload, further growth of cardiac mass allows sufficient tension to be developed for the ejection of blood yet interferes with the ejection process. To assess the ability of the left ventricle to generate pressure, developed pressure was calculated from peak systolic and end-diastolic pressures measured during aortic occlusion. We[4] have found that this measurement is not altered by the animal's sex. Significantly more pressure developed in all groups of hypertensive rats than in the normotensive rats. Thus, the pressure generating capacity of the hypertrophied left ventricle of all groups of hypertensive rats was greater than that of normotensive rats. However, even though the 18 month old rats had a substantially greater left ventricular weight than did the 6 month old rats, higher pressures did not develop in the former rats than in the latter, a finding that suggests that even this aspect of ventricular performance might have declined with age.

In summary, cardiac hypertrophy increases with age in spontaneously hypertensive rats despite the maintenance of a stable elevation of systemic arterial pressure. This hypertrophic growth of the left ventricle is associated with both a compensated and a depressed phase of cardiac performance. Young hypertensive rats with moderate left ventricular hypertrophy eject a

normal stroke volume from a normal end-diastolic volume in the presence of an increased afterload. With time and further increase in cardiac mass, systolic function is significantly diminished.

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Ventricular Function and Coronary Hemodynamics in Hypertensive Heart Disease

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Left ventricular function, wall geometry and coronary hemodynamics were analyzed in 114 patients with essential hypertension during diagnostic left heart catheterization, left ventriculography and coronary arteriography. Results of the study were as follows:

1. Left ventricular function (as assessed from the cardiac index, stroke volume index, ejection fraction, mean velocity of circumferential fiber shortening, mean normalized systolic ejection rate, isovolumic indexes) was normal in patients with hypertensive hypertrophy, even with a large increase in muscle mass and even in the presence of concomitant coronary artery disease. Left ventricular function was impaired when regional contraction abnormalities or ventricular dilatation, or both, occurred and was inversely related to both cardiac size and systolic wall stress.

2. Coronary blood flow (+18 percent), coronary resistance (+38 percent) and myocardial oxygen consumption ($M\dot{V}O_2$) (+21 percent) were increased in essential hypertension. Coronary reserve was reduced even in hypertensive hypertrophy without evidence of coronary artery disease. $M\dot{V}O_2$ per mass unit was directly correlated with systolic wall stress per cross-sectional area of the left ventricular wall.

3. The appropriateness of left ventricular hypertrophy may be defined by the relation between pressure, mass to volume ratio and systolic wall stress. In hypertensive heart disease at least two types of inappropriate left ventricular hypertrophy occur: (a) low stress hypertrophy, with an increased mass to volume ratio, with normal left ventricular function and with normal or reduced $M\dot{V}O_2$; and (b) high stress hypertrophy, with normal or low mass to volume ratio, impaired left ventricular function and increased $M\dot{V}O_2$. It is concluded that the appropriateness of left ventricular hypertrophy, as a result of mass to volume ratio and stress, is a major determinant of left ventricular performance and of myocardial oxygen consumption, and that the individual history of left ventricular pressure load specifically may influence left ventricular function.

Essential hypertension is the most frequent form of left ventricular pressure load in man.[1–4] Its cardiac consequences closely depend on the degree of myocardial hypertrophy and on the progression of coronary artery disease.[3,4] There have been relatively few reports[5,6] on cardiac performance in human hypertension, in part because the disease is often asymptomatic and not thought to justify left ventricular catheterization. This study was therefore undertaken to investigate the cardiac manifestations of essential hypertension with special reference to left ventricular function, wall geometry, coronary hemodynamics and myocardial energy demand.

Methods

Study patients: The results reported are based on a total of 201 patients, 114 of whom were hypertensive. The latter all had essential hypertension (World Health Organization classification I to III). Left ventriculography and coronary

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angiography were performed during otherwise indicated invasive procedures (cardiac catheterization or renal arteriography). On the basis of these tests, the first 88 patients were classified into four subgroups as follows:

Group I: 15 patients with compensated essential hypertension (New York Heart Association[7] [NYHA] class 0/I), without coronary artery disease (mean age 44 years).

Group II: 32 patients with compensated essential hypertension (NYHA class 0/I) with 75 percent or greater stenosis of the left anterior descending coronary artery without regional wall contraction abnormalities (mean age 41 years).

Group III: 29 patients with essential hypertension with regional wall motion abnormalities (hypokinesia and akinesia) due to coronary artery disease (mean age 39 years).

Group IV: 12 patients with decompensated essential hypertension (NYHA class IV) on the basis of global wall contraction abnormalities (mean age 49 years).

Coronary hemodynamics were specifically investigated in an additional group of 26 hypertensive patients (mean age 42.5 years). Of the 114 hypertensive patients, the majority (78) were untreated; in the remaining 36, all drugs were discontinued 8 to 14 days before examination. Treatment in the latter had mainly consisted of diuretic drugs, clonidine or reserpine; six had been taking propranolol. No significant differences in hemodynamic, coronary and ventricular responses could be detected between untreated subjects and those who discontinued therapy.

The results in hypertensive patients were compared with findings in the following groups of subjects: (1) 12 patients with no evidence of cardiovascular disease (normal subjects); (2) 36 normotensive patients with coronary artery disease; (3) 12 patients with hypertrophic obstructive cardiomyopathy; (4) 15 patients with aortic stenosis (6 with NYHA class I/II disease, 9 with class III/IV disease); and (e) 12 patients with aortic incompetence (NYHA class III/IV).

Angiocardiographic studies: No premedication was used. After left ventricular pressures were recorded, quantitative ventriculography was performed in all patients using power injections (Contrac) of 40 to 60 ml of 76 percent meglumine sodium diatrizoate. Methodologic details have been published previously.[3,4,6,8] Left ventricular volume was calculated by the method of Bunnell, Greene and others,[9–16] using the formula $V = \pi LM^2/6$, where V = volume, L = longest measured chamber axis and M = internal transverse diameter at the mid point of L. L was taken directly from the ventriculogram and M was derived from the area (F) of the left ventricle ($M = 4 \cdot F/\pi \cdot L$). Volume measurements were obtained both in end-diastole as well as in each frame during systole until the peak value of systolic circumferential wall stress was attained.[15]

Peak systolic wall stress (T_{syst}) was determined from intraventricular pressure, radius and wall thickness by the use of the Laplace equation ($T_{syst} = p \cdot r/2d$), where ρ = peak systolic developed pressure, p = internal left ventricular radius derived from volume measurements and d = wall thickness. Wall thickness (d) was recorded frame by frame as the average thickness of a 4 cm segment of the free wall on the anterior projection, one third of the distance from the apex.[9] Each value for intraventricular pressure, ventricular radius and ventricular wall thickness was determined for calculation of instantaneous wall stress until the peak value of systolic circumferential wall stress was obtained.

Left ventricular and aortic pressures were measured through fluid-filled catheters (pigtail, Cordis) that were directly connected to pressure transducers (Statham P23Gb). The catheter system had a natural frequency above 20 hertz and a phase lag that varied linearly with frequency in this

TABLE I

Hemodynamics and Ventricular Function Values in 12 Normal Subjects and in the Four Subgroups of Essential Hypertension (EH)*

	$\bar{P}_{art}$ (mm Hg)	LVMM (g/m^2)	LVMM/$\bar{P}_{art}$ ($g/m^2 \cdot$mm Hg)	P_{LVED} (mm Hg)	EDV (ml/m^2)	LVMM/EDV (g/ml)
Normal subjects	91 ± 9	92 ± 6	1.01	10 ± 1	81 ± 6	1.14
Subgroups with EH						
I	136 ± 9†	122 ± 11‡	0.90	12 ± 2	74 ± 6	1.65
II	128 ± 6†	129 ± 14§	1.01	15 ± 4	80 ± 5	1.61
III	131 ± 3†	168 ± 16†	1.28	19 ± 7‖	112 ± 16	1.50
IV	146 ± 4†	192 ± 15†	1.32	23 ± 6‡	147 ± 17‡	1.31

	CI (liter/min per m^2)	EF (%)	dP/dt_{max} (mm Hg/sec)	Vcf (circ/sec)	T_{syst} (10^3 dynes cm^2)	$M\dot{V}O_2$ (ml/min per 100 g)
Normal subjects	3.82 ± 0.09	72 ± 2	1690 ± 90	1.62 ± 0.13	220 ± 9	7.98 ± 0.52
Subgroups with EH						
I	3.95 ± 0.08	78 ± 5	2460 ± 110†	1.71 ± 0.12	232 ± 8	8.21 ± 0.31
II	3.93 ± 0.09	69 ± 5	2400 ± 94†	1.36 ± 0.11	208 ± 19	7.13 ± 0.19
III	3.22 ± 0.10†	61 ± 6‖	2310 ± 88	0.74 ± 0.14§	256 ± 18	9.62 ± 0.34‡
IV	3.24 ± 0.11†	40 ± 8‡	2190 ± 102‡	0.44 ± 0.14§	369 ± 26†	12.8 ± 0.61§

* Statistical analysis was performed by means of the *t* test (mean ± standard error of the mean). *P* values listed in table are given for comparison of normal subjects and groups with essential hypertension. *P* values within subgroups with essential hypertension (I to IV) are as follows: P_{art} (II vs. IV, $P < 0.02$; III vs. IV, $P < 0.005$); LVMM (I vs. III, $P < 0.025$; I vs. IV, $P < 0.001$; II vs. IV, $P < 0.005$); P_{LVED} (I vs. IV, $P < 0.05$); EDV (I vs. IV, II vs. IV $P < 0.001$); CI (I vs. III, I vs. IV, II vs. III, II vs. IV, $P < 0.001$); EF (I vs. IV $P < 0.001$, II vs. IV, $P < 0.005$); V_{CF} (I vs. III, I vs. IV, II vs. III, II vs. IV, $P < 0.001$); T_{syst} (I vs. IV, II vs. IV, III vs. IV, $P < 0.001$); MVO_2 (I vs. II, I vs. III, $P < 0.005$; I vs. IV, II vs. III, II vs. IV, III vs. IV, $P < 0.001$). Significance for LVMM/P_{art} (tested against normal subjects) was $p < 0.001$ for groups III and IV; for LVMM/EDV, *P* values were $P < 0.001$ (groups I and II) and $P < 0.05$ (group III).

† $P < 0.001$.

‡ $P < 0.01$.

§ $P < 0.005$.

‖ $P < 0.05$.

CI = cardiac index; circ = circumference; dP/dt_{max} = maximal rate of left ventricular pressure development; EDV = end-diastolic volume; EF = ejection fraction; LVMM = left ventricular muscle mass; $M\dot{V}O_2$ = left ventricular oxygen consumption; P_{art} = mean arterial pressure; P_{LVED} = left ventricular end-diastolic pressure; T_{syst} = peak circumferential systolic wall stress; Vcf = mean circumferential fiber shortening.

frequency range. All pressures were referred to 0 level 10 cm above the table top. Peak first derivative of left ventricular pressure (dP/dt) was determined from resistance-capacitance differentiating units (time constant = 0.1 msec); peak dP/dt/IP was calculated by dividing the maximal rate of pressure development (dP/dt_{max}) by its corresponding isovolumic pressure (IP).

Left ventricular mass determinations were made from end-diastolic chamber dimensions, that is, from end-diastolic measurements of wall thickness and volume. Calculations were based on determination of the volume of a "shell" obtained by subtracting the adjusted end-diastolic left ventricular volume from the total volume by adding lateral wall thickness to calculated ellipsoidal chamber dimensions. The volume of that shell was converted to mass by multiplying it by the specific gravity of heart muscle.[11] The left ventricular mass to volume ratio (M/V ratio) was obtained by dividing left ventricular mass by the end-diastolic volume.

Coronary blood flow: A Goodale-Lubin catheter (Ch. 7) was inserted through the left antecubital vein and introduced into the coronary sinus for coronary sinus blood sampling and determination of coronary blood flow. Coronary blood flow was measured after right and left heart catheterization and before left ventriculography by means of the argon method with gas chromatographic analysis of argon in arterial and coronary venous blood. Details as well as a record of the accuracy of this method, which allows measurements of coronary blood flow up to 400 to 500 ml/min per 100 g, have previously been published.[17–22] The linearity of this method over the whole range of physiologically existing coronary blood flow was proved by comparisons with flowmeter and coronary sinus sampling techniques.[17,18] Argon blood concentrations were determined after extraction through a specially designed extraction chamber with use of gas chromatography (trace gas analyzer 1533 B, Varian, Darmstadt, Federal Republic of Germany). Measurements of coronary blood flow were carried out under resting conditions and during maximal coronary vasodilation. The latter was achieved by the intravenous injection of a potent coronary vasodilator (dipyridamole, 0.5 mg/kg body weight), which was given to each patient in fractions that would exert no significant effects on aortic pressure or heart rate.[18-22] Coronary vascular resistance (mm Hg/ml per min per 100 g) was determined as the ratio of coronary perfusion pressure to coronary flow; the former was calculated as mean diastolic aortic pressure minus mean left ventricular pressure.[18] Coronary vascular reserve, or coronary reserve, was defined as the ratio between coronary vascular resistance in the resting state and the resistance during maximal coronary vasodilation.[21] Left ventricular oxygen consumption (ml/min per 100 g) was determined as the product of coronary blood flow (ml/min per 100 g) and the arterial-coronary venous oxygen difference (vol percent). Arterial and coronary venous oxygen saturation levels were measured with carbon monoxide-oximetry.

Results

Central hemodynamics and left ventricular function: Mean arterial pressure was increased in hypertension by approximately 50 percent without significant differences among the four hypertensive subgroups I to IV (Table I). In contrast, left ventricular muscle mass, which is a consequence of chronic pressure overload, progressively increased from group I to group IV. Accordingly, the left ventricular mass to pressure load ratio was markedly elevated in the groups III and IV with advanced hypertension. It would be reasonable to assume that this progression of cardiac hypertrophy was related to the duration and severity of hypertensive heart disease.

End-diastolic pressure and end-diastolic volume were considerably increased in the hypertensive groups III and IV (Table I). In contrast, end-diastolic volume was nearly normal in clinically compensated essential hypertension whether or not it was associated with coronary artery disease (groups I and II), and end-diastolic pressure was only moderately elevated in these patients. The mass to volume ratio was greatly increased in compensated hypertension because of a considerable mass increase per volume, whereas the mass to volume ratio tended toward normalization in decompensated hypertension (group IV). The latter finding was attributable to a progressive increase in volume despite further augmentation of left ventricular mass. Cardiac index, stroke volume index and ejection phase indexes were normal in groups I and II, but they were depressed in hypertensive patients with wall motion abnormalities and with cardiac decompensation (groups III and IV) (Table I). The maximal rate of left ventricular pressure development (dP/dt_{max}) was increased in all groups; however, the ratio of dP/dt_{max} to its corresponding isovolumic pressure was normal in groups I (38 ± 4/sec) and II (42 ± 5/sec), and it was depressed in groups III (29 ± 4/sec) and IV (22 ± 3/sec).

Left ventricular wall dynamics: Peak systolic wall stress was inversely related to the mass to volume (M/V) ratio (Fig. 1). Stress decreased with increments in the M/V ratio, and it increased when the M/V ratio decreased. The largest mass to volume ratio occurred in patients with hypertrophic obstructive cardiomyopathy, whereas the lowest values were found in those with decompensation secondary to either pressure or volume

TABLE II

Coronary Perfusion Pressure, Arterial-Coronary Venous Oxygen Difference, Coronary Blood Flow of Left Ventricle and Coronary Resistance in Normal Subjects, in Patients With Essential Hypertension (EH) and in Normotensive Coronary Artery Disease (CAD)*

	P_{cor} (mm Hg)	$avDO_2$ (vol/]	V_{cor} (ml/min·100 g)	R_{cor} (mm Hg·min·100 g·ml^{-1})
Normal subjects (no. = 12)	82 ± 2	12.2 ± 0.1	71 ± 3	1.15 ± 0.04
EH (no. = 63)	129 ± 8†	12.9 ± 0.2	83 ± 2‡	1.57 ± 0.06†
CAD (no. = 38)	87 ± 5	12.8 ± 0.6	64 ± 3§	1.36 ± 0.09

* Note the increase of both coronary perfusion pressure and coronary resistance in essential hypertension. Arterial-coronary venous oxygen difference and, hence, coronary oxygen extraction were unchanged in the three groups.

† $P < 0.001$.

‡ $P < 0.005$.

§ $P < 0.02$.

$avDO_2$ = arterial-coronary venous oxygen difference; CAD = (normotensive) coronary artery disease; EH = essential hypertension; P_{cor} = coronary perfusion pressure; R_{cor} = coronary resistance; V_{cor} = coronary blood flow of left ventricle.

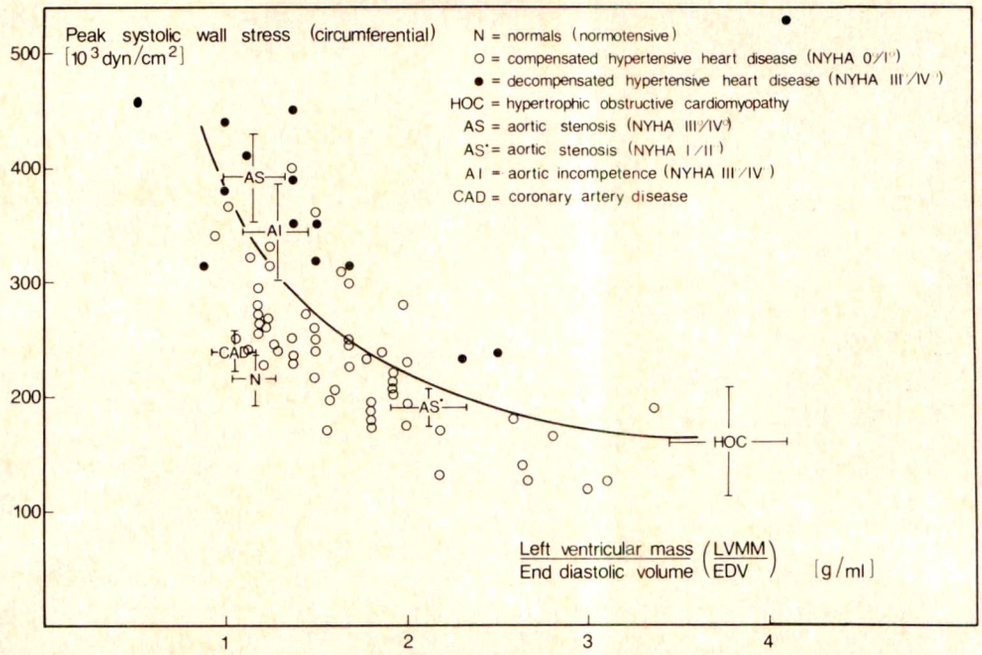

FIGURE 1. Relation between left ventricular mass to volume ratio (LVMM/EDV) and peak systolic wall stress. A decrease in wall stress with an increase in mass to volume ratio is demonstrated. The curve (= isobar for all patients with essential hypertension) was calculated by polynome fitting ($Y = 31.2 + 371.2 \times 1/X$, where Y = wall stress, X = mass to volume ratio). Note the following points: (1) normotensive normal subjects (N) and normotensive subjects with coronary artery disease have shifts to lower wall stress at comparable mass to volume ratio (= lower isobar). (2) The appropriateness of left ventricular hypertrophy in essential hypertension may be derived from the course of this curve: at a normal mass to volume ratio, an increased wall stress is present for decompensated hypertensive disease (class III or IV) (high stress hypertrophy), whereas an appropriate increase in mass to volume ratio despite an enhanced systolic pressure load may maintain normal systolic wall stress (normal stress hypertrophy). In contrast, excess augmentation of left ventricular mass out of proportion to volume may lead to a decrease in systolic wall stress (low stress hypertrophy). (3) Hypertrophic heart disease (AS, AI, HOC) may be situated within the isobaric characteristics of hypertensive heart disease, if systolic pressure is increased at comparable mass to volume ratio. (4) Left ventricular hypertrophy due to aortic stenosis may have increased wall stress (AS; III or IV) (high stress hypertrophy) or normal wall stress (AS*, I or II) (normal stress hypertrophy), and wall stress may be even reduced, despite increased intraventricular systolic pressure load in hypertrophic obstructive cardiomyopathy (low stress hypertrophy). NYHA = New York Heart Association.

overload.[23] Data from patients with concentric left ventricular hypertrophy due to either essential hypertension or aortic stenosis fell within this general correlation, whereas data from normotensive subjects were shifted to lower systolic stress for equal mass to volume ratio, that is, to a lower isobaric relation.

With the increase in systolic wall stress, there occurred a decrease in left ventricular ejection fraction (Fig. 2). Patients with the highest wall stress had the lowest ejection fraction and lowest ejection phase indexes (velocity of circumferential fiber shortening and normalized systolic ejection rate).

Coronary hemodynamics (Table II); Left ventricular coronary blood flow was increased in essential hypertension by a mean of 18 percent ($P < 0.005$), whereas coronary perfusion pressure (that is, mean diastolic aortic pressure minus mean diastolic left ventricular pressure) was increased by 56 percent. In consequence, coronary vascular resistance was significantly ($P < 0.001$) increased by 38 percent. Arterial-coronary venous oxygen difference in hypertensive patients was not different from normal values. Coronary reserve, which averaged 4.8 in normal subjects, was significantly ($P = 0.01$) reduced in those with essential hypertension (Fig. 3). In hypertensive patients with concomitant coronary artery disease (group II), the coronary reserve was quantitatively similar to that found among normotensive patients with coronary artery disease. However, even in the absence of evident coronary artery disease, patients with essential hypertension (group I) had a significant reduction in coronary reserve; this averaged 34 percent below normal ($P = 0.01$).

Left ventricular oxygen consumption: The left ventricular oxygen consumption ($M\dot{V}O_2$) was increased only in the hypertensive patients of groups III and IV (Table I). Within the total group of hypertensive patients, no correlations were found with either aortic or intraventricular pressure levels, with isovolumic velocity or with ejection phase indexes. However, comparison of data from different groups showed some relation between oxygen consumption per 100 g left ventricular weight and systolic stress per cross-sectional area unit (Table I). The correlation between these two values was significant ($r = 0.78$, $P < 0.001$) (Fig. 4); data from patients with aortic valve lesions (stenosis or regurgitation) as well as those from patients with coronary artery disease fell along the regression line (Fig. 4).

Discussion

Left ventricular function: This study has shown that left ventricular function in hypertensive heart

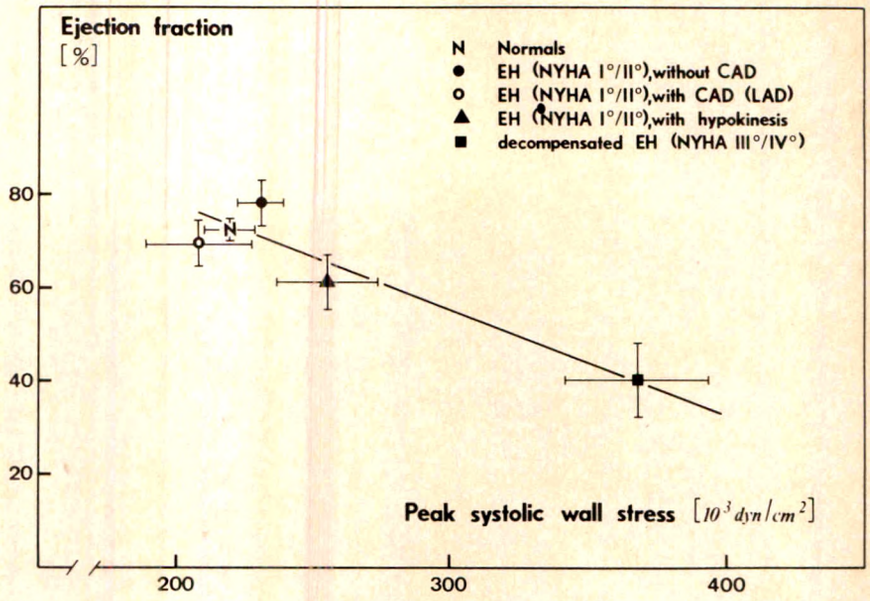

FIGURE 2. Relation between peak systolic wall stress and the left ventricular ejection fraction. Note the decrease in ejection fraction upon increase in systolic wall stress. Similar stress-dependent decrease in left ventricular function indexes was found for the mean velocity of circumferential fiber shortening (Vcf) and for mean normalized systolic ejection rate. CAD = coronary artery disease; EH = essential hypertension; LAD = left anterior descending coronary artery disease; NYHA = New York Heart Association.

disease may remain normal in the presence of marked left ventricular hypertrophy (group I) even when associated with coronary arterial stenosis (group II) (Table I). Thus, an increase in left ventricular mass due to chronic pressure overload need not necessarily be associated with impaired left ventricular function.[3,4] The data on hypertensive hypertrophy in our patients appeared to diverge in this respect from data reported in other types of pressure-induced left ventricular hypertrophy (such as aortic stenosis or coarctation of aorta); in the latter conditions, studies by others[24–26] indicated that depression of ventricular function was the rule, as evidenced by decreases of both isovolumic and ejection phase indexes. Normal contractile behavior of hypertrophied myocardium was also reported in rats with spontaneous hypertension.[27–29] It may be reasonable to assume that the specific circumstances of the hypertensive disease as well as the type of chronic pressure overload play an important role in the ventricular performance in hypertensive hypertrophy.

Stress and function: Left ventricular function in hypertensive heart disease depended closely on heart size and, with comparable systolic pressure, on the systolic stress that is imposed at the left ventricular wall. Peak systolic wall stress and left ventricular function were inversely related (Fig. 2). Systolic wall stress may

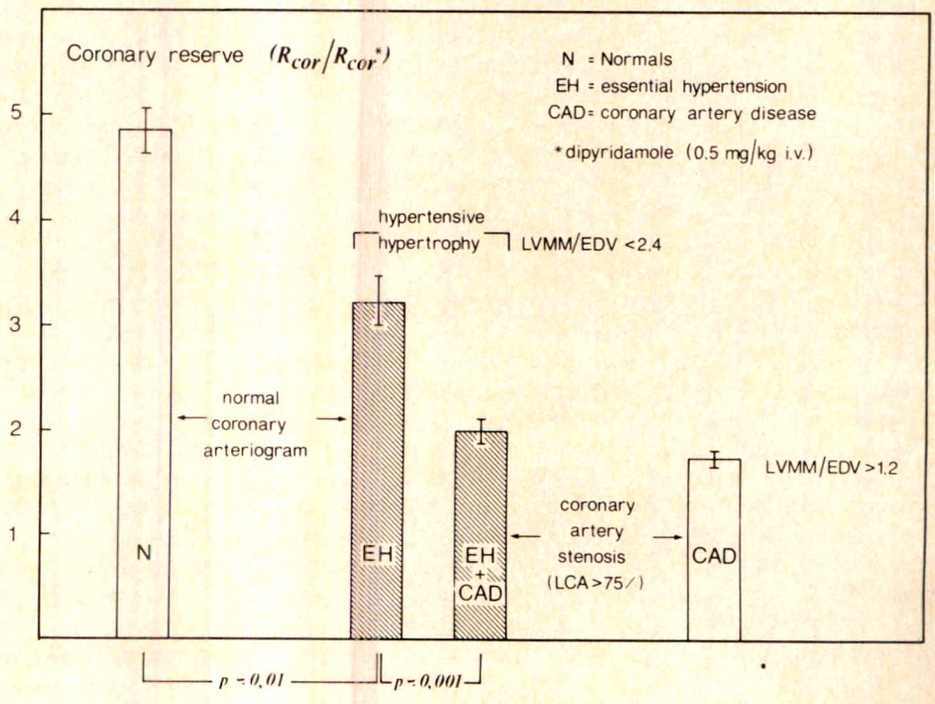

FIGURE 3. Coronary reserve, defined as the ratio of coronary resistance (R_{cor}) under control conditions and coronary resistance under maximal coronary dilatation (R_{cor}^*), in normal subjects (N), in those with essential hypertension (EH) with a normal coronary arteriogram, in those with essential hypertension with coronary arterial stenosis and in normotensive patients with coronary artery disease (CAD). Note the decreased coronary reserve even in hypertensive hypertrophy with normal coronary arteriogram. i.v. = intravenously; LCA = left coronary artery; LVMM/EDV = left ventricular mass to volume ratio; p = probability.

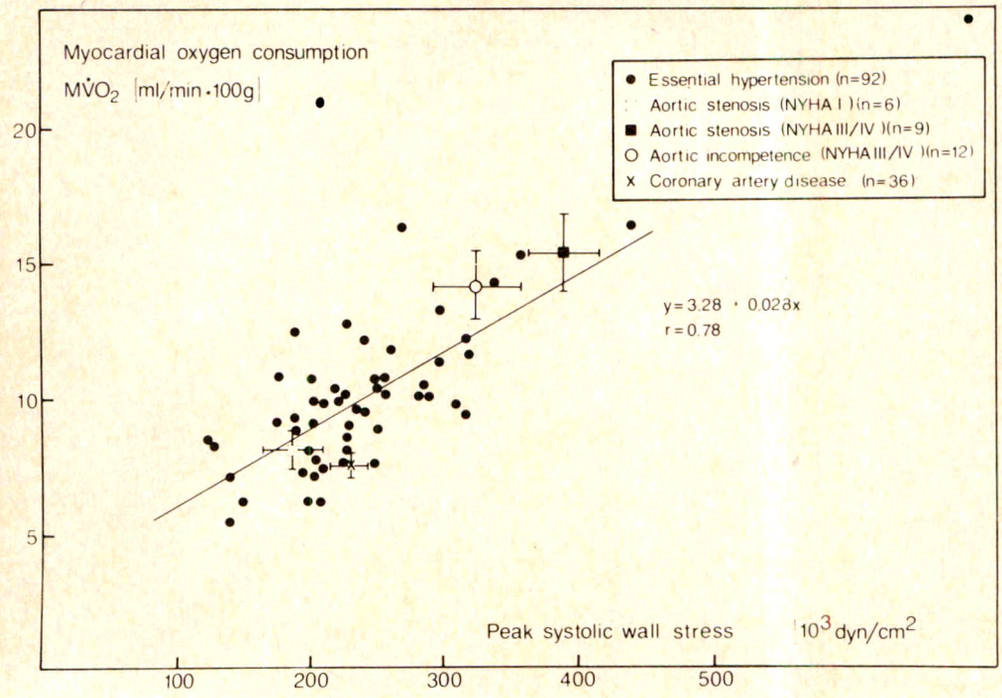

FIGURE 4. Relation between peak systolic wall stress per cross sectional area unit (**abscissa**) and the myocardial oxygen consumption per 100 g of left ventricular weight unit ($M\dot{V}O_2$, **ordinate**). Note the following: (1) $M\dot{V}O_2$ in essential hypertension may be normal, increased or even decreased, the amount of myocardial energy demand being closely related to systolic wall stress, and hence to both systolic pressure load and to the appropriateness of left ventricular hypertrophy. (2) Extrapolation of regression to zero stress results in an intercept of 3.28 ml/min × 100 g. This value, although somewhat higher, corresponds quite well with the oxygen consumption of the empty beating heart. n = number of subjects; NYHA = New York Heart Association; r = correlation coefficient.

be considered the fundamental correlate of the left ventricular afterload. Therefore, the characteristic inverse relation between stress and function underlines the important influence of systolic wall stress or afterload, respectively, on left ventricular performance in hypertensive heart disease. Since other factors, such as contractility and heart rate, may influence left ventricular performance, the steepness of regression between stress and function may presumably be modified at various contractile states and heart rates.

Stress and myocardial oxygen consumption: The close relation between systolic wall stress and myocardial oxygen consumption also underlines the importance of wall stress for myocardial aerobic energy demand. Data obtained showed an average increase in myocardial oxygen consumption of 2.8 ml/min per 100 g for each 100 unit (10^3 dynes/cm^2) increase in systolic wall stress. This ratio held for compensated (class I) as well as for decompensated (class IV) hypertensive heart disease, which indicates that stress-dependent alterations in myocardial energy demand are similar in the two types of hypertensive hypertrophy, despite their presumably different contractile state. Because heart rate did not differ significantly between the two, both wall stress and contractility are the main factors to be considered in this situation in regard to myocardial oxygen consumption.

Increased myocardial oxygen consumption was found in high stress hypertrophy that was regularly associated with impaired left ventricular function and contractile state, as evidenced by depressed isovolumic and ejection phase indexes (Table I). On the other hand, normal or low myocardial oxygen consumption was present in normal or low stress hypertrophy, and this latter was regularly associated with normal left ventricular function. There is little question that contractile state influences myocardial oxygen consumption, especially with regard to acute inotropic interventions. This statement is presumably also valid for chronic hypertrophic heart disease in relation to acute inotropic interventions. However, in chronic hypertensive heart disease, the oxygen consumption of the heart is mainly governed quantitatively by alterations in wall stress. This phenomenon obviously reflects a mismatch between stress and contractility in favor of a predominant influence of stress on myocardial energy demand in chronic hypertrophic heart disease.

Coronary reserve: The increase in coronary resistance under resting conditions (Table II) can presumably be related to increased tone of the coronary vascular bed in essential hypertension. However, there may be at least four possible reasons for the reduced coronary reserve: (1) In theory, the responsiveness to dipyridamole, which was used as the test agent, could be altered; however, no alteration in coronary sensitivity to dipyridamole-induced coronary dilatation has been documented to date.[18–21] (2) The hypertrophied ventricular wall could restrict coronary dilatation. However, in aortic stenosis as well as in hypertrophic obstructive cardiomyopathy normal coronary reserve has been found with a normal coronary arteriogram.[30,31] (3) Increased coronary vascular tone could limit complete coronary dilatation. Because the coronary resistance is already increased in essential hypertension at rest, the minimal coronary resistance after maximal coronary dilatation would be increased, even with normal coronary reserve. Thus, a functional increase in the tone of coronary resistance vessels could limit coronary reserve.

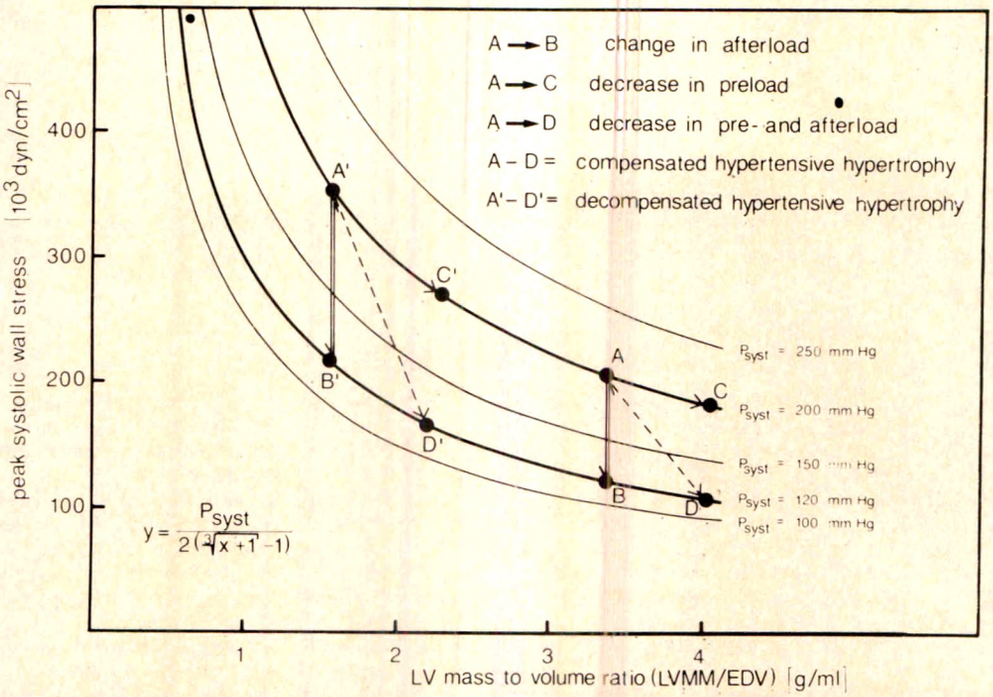

FIGURE 5. Diagrammatic representation of concept of the relation between mass to volume ratio (**abscissa**) and peak systolic wall stress (**ordinate**) for different isobaric conditions (for original data, see Fig. 1). Calculation of isobars was performed with use of the Laplace equation. The lack of parallelism and curvature of these isobaric relations implies that systolic pressure (P_{syst}) changes occurring at points with a high mass to volume ratio lead to fewer stress changes than the same systolic pressure variations at a low mass to volume ratio. An equal increase in systolic pressure, for example, from 120 to 200 mm Hg (that is, from B to A), at a mass to volume ratio of 3.5 leads to a stress increase of only 80 units (10^3 dynes/cm^2). However, with the same increase in pressure (that is, from B′ to A′) at a mass to volume ratio of 1.5, systolic wall stress is considerably increased by 160 units. The same consequences are valid for therapeutically induced pressure reductions (from A′ to B′, and from A to B, respectively). This means that the increase in systolic wall stress at a given rise in systolic pressure in hypertensive heart disease is greater in the dilated than in the nondilated heart. Conversely systolic and metabolic unloading of the left ventricle at equal pressure reduction is greater or more effective in a dilated than in a nondilated heart. This relation between mass to volume ratio and stress emphasizes the importance of heart size and systolic wall stress on changes in stress and, hence, in ventricular function and myocardial energy demand.

(4) Finally, structural involvement of the small coronary arteries[32,33] could be responsible for the reduction in coronary reserve.

The reduction in coronary reserve in hypertensive hypertrophy without coronary arterial stenosis may indicate increased ischemic risk and decreased coronary reserve capacity under stress conditions even in hypertensive patients without coronary disease. This may help to explain the increased risk of secondary lesions of the myocardium (such as coronary insufficiency, myocarditis and congestive heart failure) in patients with hypertensive heart disease.

Appropriateness of hypertrophy—clinical implications: With regard to the relation between the mass to volume ratio and wall stress, at least three possibilities of development of different degrees of hypertrophy may occur in the patient with chronic hypertensive heart disease (Fig. 1):

1. Appropriate hypertrophy, that is, normal stress hypertrophy, which results in a normal systolic wall stress even with an extreme pressure load; this is the result of appropriate increase in the mass to volume ratio parallel to pressure load (concentric hypertrophy).

2. Inappropriate hypertrophy with low stress, which results from marked increase in left ventricular mass out of proportion to intraventricular volume (irregular ventricular hypertrophy, such as hypertrophic obstructive cardiomyopathy).

3. Inappropriate hypertrophy with high stress, which is characterized by excess dilatation out of proportion to ventricular mass development (eccentric hypertrophy, such as decompensated hypertensive heart disease).

Thus, at least two forms of inappropriate hypertrophy may occur in chronic hypertrophic heart disease.

The appropriateness of degree of left ventricular hypertrophy determines to a large extent the heart's capacity to tolerate hypertensive emergencies as well as its potential for functional improvement after antihypertensive therapy (Fig. 5). Dependent on the initial stress situation, equal reduction in systolic pressure (A→B, A′→B′) can lead to marked differences in decrease of systolic wall stress and hence in left ventricular afterload. Likewise, different changes in stress can occur relative to initial stress when either the preload is affected (A→C, A′→C′) or when both afterload and preload are altered (A→D, A′→D′). A therapeutic reduction in afterload would have a greater "unloading effect" on the left ventricle in decompensated hypertensive heart disease; contrariwise, an increase in arterial pressure would lead to earlier cardiac failure in high

stress hypertrophy than it would in low stress hypertrophy (Fig. 5). Accordingly, patients with high stress hypertrophy have limited stress reserve[34,35] and enhanced responsiveness to cardiac unloading interventions when compared with patients with low stress hypertrophy.

From the point of view of energetics, an equal pressure rise may lead to a greater increase in myocardial oxygen consumption in high than in low stress hypertrophy. This may be expected from the different changes in systolic wall stress in the two types of hypertrophy (Fig. 5). Reciprocal behavior is valid for a therapeutically induced decrease in pressure. Thus, hypertensive heart disease with a large initial wall stress (high stress hypertension) is associated not only with impaired cardiac function at rest, but also with a left ventricle that may have less metabolic reserve and greater vulnerability to stress.[36]

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Cardiac Load and Function in Hypertension

Ultrasonic and Hemodynamic Study

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On the basis of echocardiographic measurements, 46 patients with established, uncomplicated primary hypertension (diastolic pressure = 100 mm Hg) were classified as: those with a normal-sized heart (Group I, 13 patients); those with left ventricular concentric hypertrophy (Group II, 19 patients); and those with left ventricular hypertrophy and enlargement (Group III, 14 patients). Eighteen age-matched healthy subjects were investigated as the controls. The function of both the left and right ventricle, evaluated by the stroke index-filling pressure relation and by the mean rate of ejection, was maintained in Group I, augmented in Group II and reduced in Group III, in comparison with the controls.

Left ventricular mean rate of circumferential fiber shortening (V_{cf}) was normal in Group I, significantly augmented in Group II and definitely reduced in Group III. It could not be established whether the divergent variation from normal of the V_{cf} in Groups II and III reflected opposite changes in ventricular contractility or in afterload (wall stress during ejection), or both. However, the parallel functional pattern of the right and left ventricle in these two groups suggests a functional interdependence of the two sides which cannot be interpreted in terms of afterload but is best explained by changes in the contractile state of the whole heart.

Afterload is a major determinant of left ventricular function in hypertension. Afterload represents the stress on the myocardium as it is shortening. This stress is a function of the intraventricular pressure during ejection, the radius of the chamber and the thickness of the wall. The ventricular systolic pressure is therefore but one component of afterload. A given systolic pressure due to a high systemic vascular resistance would generate a greater afterload than the same pressure due to a high stroke volume, for in the latter case the radius of the chamber would be reduced more during systole. In addition, at comparable levels of systolic pressure and vascular resistance, afterload may be reduced when ventricular hypertrophy develops or it may be enhanced when the cavity becomes enlarged. Therefore, systolic pressure, vascular resistance, cavity size and ventricular wall thickness should all be considered whenever the function of the hypertensive left ventricle is to be assessed.

In earlier clinical studies carried out by others[1,2] and by our laboratory[3] it was reported that the performance of the hypertensive hypertrophied heart is impaired. There are some reasons, however, to reconsider the validity of this conclusion. In fact, conventional electrocardiographic criteria used in previous reports to define hypertrophy present obvious limitations that derive from the prevalence of false-positive[4] and false-negative[5] diagnoses. A substantial number of false-positive and false-negative results are also obtained when standard chest radiography is used to assess left ventricular enlargement.[6] In addition, the use of chest X-ray criteria of left ventricular enlargement to diagnose hypertrophy[2] evidently precludes a separate analysis of concentric hypertrophy and, respectively, dilatation of the left ventricle.

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Echocardiography offers the following advantages: Positive findings of concentric hypertrophy are much more frequent with ultrasound than with electrocardiography or chest roentgenography[7]; and it integrates intravascular methods to evaluate cardiac function and wall stress.[8] In this study a large hypertensive population was investigated by a combination of these two methods.

Methods

Patients

Forty-six men in the hospital with uncomplicated primary arterial hypertension (blood pressure above 179/99 mm Hg) were the subjects of this study. Criteria for their selection were: age less than 60 years; absence of history or signs referable to heart failure, pulmonary disease, valvular lesions, angina pectoris, old myocardial infarction or idiopathic myocardial disease in addition to hypertension; normal serum electrolyte concentration; regular sinus rhythm without conduction abnormalities; no digitalis at any time in the past or antihypertensive therapy for at least 1 month before entry; no priority need for therapy; and ability to record a technically satisfactory left ventricular echocardiogram. Subjects were not included who exhibited a ratio of septal to posterior wall thickness greater than 1.3 or abnormal intraventricular septal motion. To obtain this group of subjects who met criteria for inclusion into the study, 140 hospitalized hypertensive patients were screened.

Healthy volunteers or patients in the hospital without signs of circulatory disorders and without medication that could interfere with their cardiovascular function were also studied as the controls (18 patients). All subjects gave free consent to the investigation with full knowledge of the procedures to be undertaken.

Hypertensive patients were divided into three groups according to the following echocardiographic criteria: Group I (normal heart), 13 subjects in whom the interventricular septum, posterior wall thickness and end-diastolic left ventricular minor axis were within the standard deviation of controls; Group II (concentric hypertrophy), 19 patients with normal or, more often, reduced left ventricular minor axis in whom wall thickness (both posterior wall and septum) exceeded standard deviation of control; and Group III (hypertrophy associated with left ventricular enlargement), 14 subjects showing wall thickness within standard deviation of Group II and end-diastolic minor axis exceeding standard deviation of the same group. Examples of the echocardiographic characteristics of each hypertensive group are reproduced in Figure 1.

Hemodynamic Methods

One week after admission, during which the diagnosis of essential hypertension was made, circulatory measurements were taken in the fasting state, in the supine position, without premedication. A no. 7 flow-directed Swan-Ganz catheter was inserted into an antecubital vein and floated, under fluoroscopy, to the pulmonary artery or advanced to the wedge position. A no. 6 polyethylene radiopaque catheter, introduced percutaneously into a brachial artery and advanced to the root of the aorta, was used to monitor arterial pressure and to sample blood for cardiac output. Reproducible dye dilution curves were obtained by a Gilford densitometer after rapid injection of indocyanine green dye, 5 mg, into the main pulmonary artery. The area under each dye-dilution curve was measured by a planimeter; cardiac output was calculated by the standard Hamilton method. Pressures were determined with Statham P23de and P23db strain gauge transducers which were balanced against atmospheric pressure. The zero reference level for pressure readings was 5 cm below the sternal angle. Mean pressures were obtained by electronic damping. The criteria for a satisfactory pulmonary artery wedge pressure were: change from the typical pulmonary artery pressure waveform to the typical pulmonary artery wedge pressure waveform on inflation of the balloon catheter. The pulmonary artery wedge pressure was characterized by distinct *a* and *v* waveforms, with the *v* wave occurring after the T wave of the electrocardiogram. Left ventricular end-diastolic pressure was estimated by the *a* wave of the wedge pressure tracing.

Measurements of right and left ventricular ejection times were obtained, respectively, by recording (on an eight channel Gould-Brush ink recorder), at a paper speed of 100 mm/sec, of pulmonary and aortic pressure tracing (from the beginning upstroke to the trough of the incisura). Both intervals were calculated from the mean of measurements on five consecutive beats, each read to the nearest 5 msec. The right and left mean

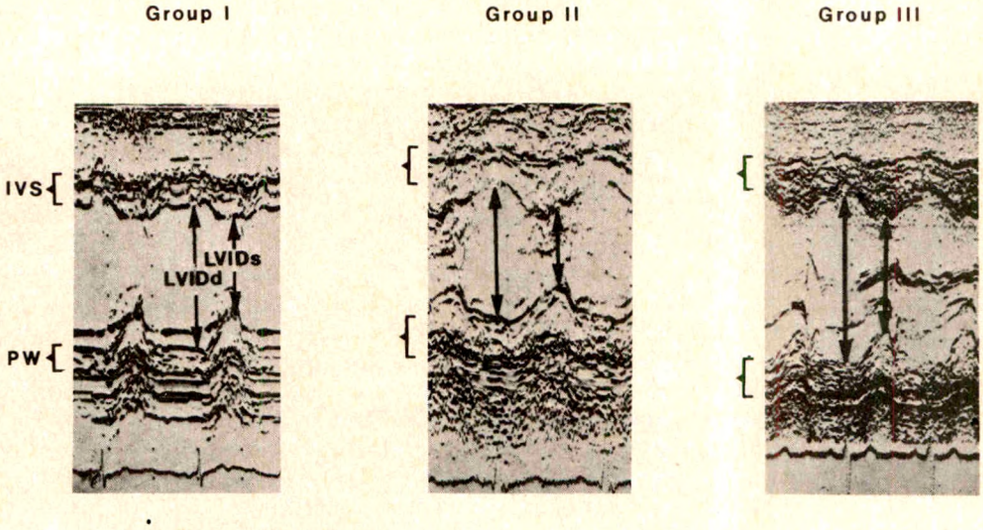

FIGURE 1. Left ventricular dimensions used for calculation of ejection phase indexes. Left, Group I; middle, Group II; right, Group III. IVS = interventricular septum; LVIDd = left ventricular internal diameter at end-diastole; LVIDs = left ventricular internal diameter at end-systole; PW = posterior wall.

rates of systolic ejection (index) were determined by dividing the stroke index by the right and left ventricular ejection times, respectively.

Systemic vascular resistance (in dynes sec cm^{-5}) was calculated from the following formula: $SVR = \overline{AP} - \overline{RAP} \times 1332 \times 60/CO$ (ml/min) where $\overline{AP}$ is the mean arterial pressure, $\overline{RAP}$ is the mean right atrial pressure and CO is the cardiac output.

Ultrasonic Methods

Echocardiography was performed with an ECHO-Cardio-VISOR (Organon Teknika) ultrasound unit. Left ventricular ultrasound measurements were taken by the technique described by Feigenbaum et al.[9] Patients were recumbent in a slight lateral decubitus position with 20 degrees elevation[9] of the head; the transducer was placed in the third or fourth left sternal interspace and was directed posteriorly and medially until the characteristic pattern of mitral valve motion was observed. The ultrasonic beam was then directed laterally and slightly inferiorly to locate a plane in which the motion of the interventricular septum and the left ventricular posterior wall components (endocardium and epicardium) could be detected simultaneously. These movements were displayed in a time-motion mode and recorded by a Honeywell strip chart recorder at a paper speed of 50 mm/sec. The tip of the mitral valve was chosen as an anatomic landmark which provided the best reproducible reference point along the left ventricular long axis for comparing quantitative measurements in different hearts.

The left ventricular internal dimensions were measured at end-diastole simultaneously with the R wave of the electrocardiogram, and at end-systole at a time when posterior wall and septum maximally approached each other; the distance was taken from the endocardial echo of the posterior wall to the echo of the left side of the septum. The thickness of the left ventricular posterior and intraventricular septal walls was estimated by measuring the distance between the endocardial and epicardial echoes of the posterior wall and, respectively, between the right and left endocardial echoes of the septum, at end-diastole. From these measurements left ventricular circumferential wall stress (CWS) and mean velocity of circumferential fiber shortening (V_{cf}) were calculated.

Circumferential wall stress at the time of aortic valve opening was taken as an index of left ventricular preejection afterload, and estimated by the formula of Sandler and Dodge,[10] and modified by Ratshin et al.[11]: $CWS = P\,D/2/h\,(1 - D)/8(D + h)$ where P is the aortic end-diastolic pressure (dynes cm^2), D is the ultrasonically measured ventricular internal minor dimension (cm) and h is the ultrasonically measured ventricular wall thickness (cm). The normalized mean velocity of circumferential fiber shortening (circ/sec) was derived from the equation of Fortuin et al.[12]: $V_{cf} = D_D - S_D/LVET \times D_D$, where D_D is the end-diastolic diameter, S_D is the end-systolic diameter and LVET is the left ventricular ejection time.

All measurements were carried out in the steady state, which was considered to be achieved when patients felt comfortable, when heart rate and pressures had definitely stabilized; in each case, however, measurements were commenced at least 30 minutes after completing the endovascular procedures. These determinations were performed twice, at 15 minute intervals; the average of the two measurements was taken as the representative value of each subject.

Statistical significance of the differences between the groups was evaluated through the analysis of variance.

Results

Ventricular dimensions and wall stress: Age and body surface area were comparable in the hypertensive patients and not significantly different from those in the controls. The echocardiographic measurements are reported in Table I. The averages of systemic and pulmonary arterial pressures (systolic and diastolic), heart rate and left and right mean rate of ejection are presented graphically in Figure 2. Systemic and pulmonary arterial pressures were significantly augmented ($P < 0.01$) in the three hypertensive groups. In each of them heart rate was similar to that of the control subjects. The mean rate of systolic ejection of either ventricle was comparable to normal in Group I, but it did increase in Group II ($P < 0.05$) and decrease in Group III ($P < 0.01$). These differences were related to larger stroke index and shorter time of ejection in Group II and, respectively, to smaller stroke index and longer ejection period in Group III, in comparison with the control subjects. Figure 3 illustrates the relation in each group between mean velocity of circumferential fiber shortening (V_{cf}), and, respectively, circumferential wall stress and systemic vascular resistance. Because of the nature of the formula for wall stress used in this study, the elevated aortic end-diastolic pressure in Group I accounted for the enhancement in circumferential wall stress as compared with normal. In Group II, despite the elevated aortic end-diastolic pressure, circumferential wall stress was comparable with normal stress; this was related to the increased wall thickness associated with a normal or reduced left ventricular minor axis. In Group III, because both aortic diastolic pressure and left ventricular dimensions were augmented, circumferential wall stress was definitely elevated. The V_{cf} was normal in Group I, augmented in Group II ($P < 0.01$) and reduced in Group III ($P < 0.01$). Systemic vascular resistance was increased similarly in Groups I and II and by a larger extent in Group III.

Stroke index and filling pressures: Figure 4 reports the relation between stroke index and filling pressure of the right (right ventricular end-diastolic pressure) and left (*a* wave of the pulmonary wedge pressure tracing) ventricles. In Groups II and III the filling pressure of the left ventricle was similar and significantly higher than normal; however, its relation to stroke volume was shifted upward in the former and down-

TABLE I

Echocardiographic Values (averages and standard deviations)

	LV Posterior Wall Thickness (mm)	LV Septal Wall Thickness (mm)	LV Internal Dimensions (mm)	
			D_D	S_D
Control subjects (no. = 18)	9.4 (1.5)	9.7 (1.2)	47.6 (1.5)	32.2 (2.5)
Hypertensive Group I (no. = 13)	9.9 (1)	9.8 (1.3)	46.5 (3.1)	31.2 (4.6)
Hypertensive Group II (no. = 19)	13.8* (1.5)	13.9* (1.1)	44.1* (3.8)	25.7* (5.2)
Hypertensive Group III (no. = 14)	13.3* (1.6)	13.6* (1.4)	55.4† (6)	46.5† (8.3)

* = differences from control subjects significant at $P < 0.01$.
† = differences from hypertensive Group II significant at $P < 0.01$.
LV = left ventricular; Group I = normal-sized heart; Group II = concentric hypertrophy; Group III = hypertrophy plus enlargement.

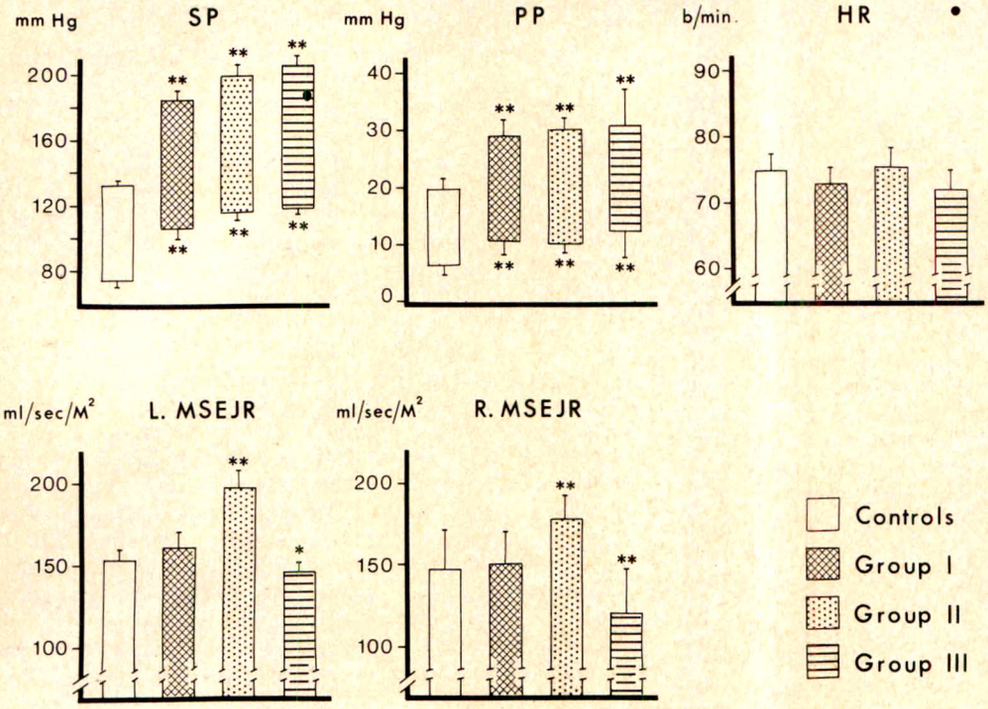

FIGURE 2. Hemodynamic functions in 18 normal control subjects and in three groups of patients with essential hypertension: Group I, 13 patients with a normal-sized heart; Group II, 19 patients with left ventricular concentric hypertrophy; Group III, 14 patients with hypertrophy associated with left ventricular enlargement. **Bars** represent the mean for the group (SEM). * and ** indicate P values of <0.05 and <0.01, respectively, for differences between the hypertensive groups and the controls. HR = heart rate; L. MSEJR and R. MSEJR = left and right mean rate of systolic ejection, respectively, PP = pulmonary arterial pressure (systolic and diastolic); SP = systemic arterial pressure (systolic and diastolic).

ward in the latter. The same pattern was observed in the right side of the heart.

Discussion

The accuracy of the echocardiographic method for measuring ventricular dimensions and wall thickness has been validated in previous reports.[9,13] it seems reasonable to consider that the hypertensive groups in this study were characterized by actual differences in left ventricular structure.

Left ventricular performance in hypertension: Several aspects of cardiac and peripheral hemodynamics differentiate hypertensive from control subjects as well as one hypertensive group from another. Since the performance of the left ventricle results from interaction of preload, afterload, contractility and im-

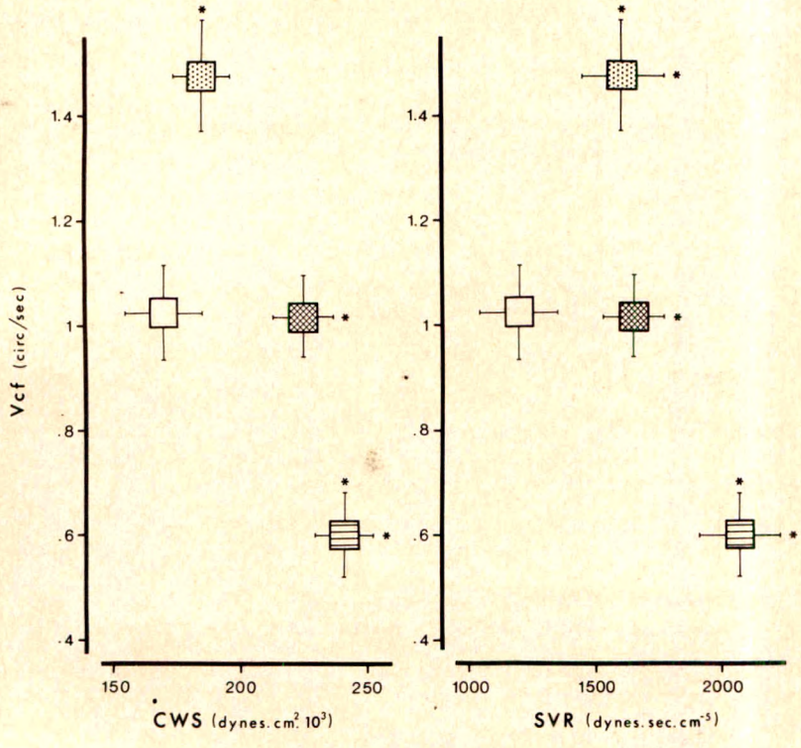

FIGURE 3. Relation between left ventricular mean velocity of circumferential fiber shortening and circumferential wall stress (**left**) and systemic vascular resistance (**right**), in the control subjects and in the three hypertensive groups. Groups are identified by the same symbols used in Figure 2. CWS = circumferential wall stress; SVR = systemic vascular resistance; Vcf = mean velocity of circumferential fiber shortening; * indicates differences from control subjects significant at $P<0.01$.

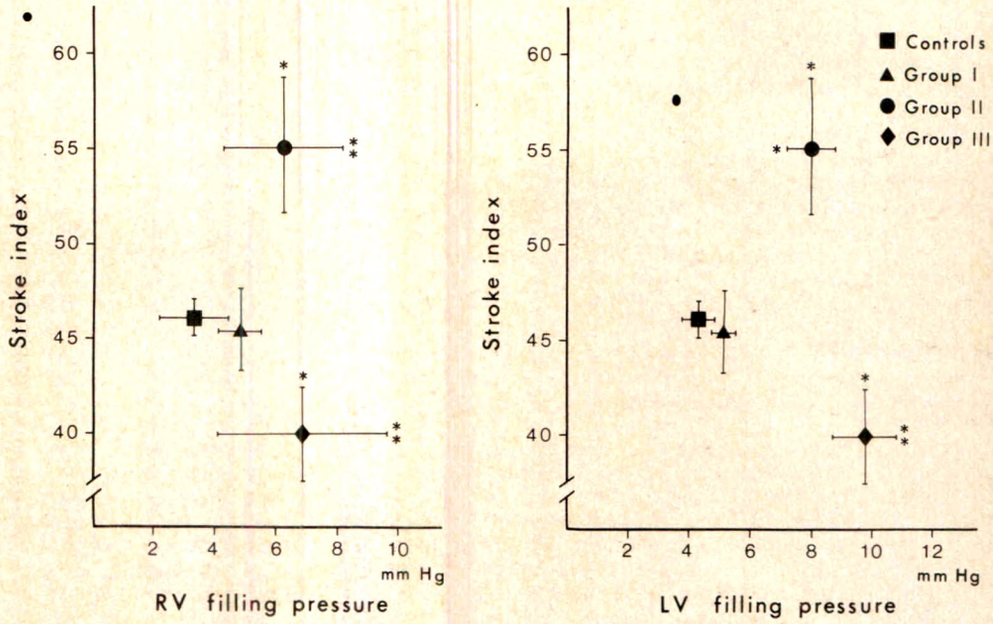

FIGURE 4. Relation between filling pressure and stroke index of the right (RV) and left ventricle (LV) in control subjects and in the three hypertensive groups. Mean and standard errors of the mean values are shown. * and ** indicate differences from control groups significant at $P < 0.05$ and $P < 0.01$, respectively.

pedance to ejection, the interplay of these factors should be considered whenever ventricular performance is to be estimated.

Upward displacement from normal in Group II and downward displacement in Group III of the stroke index-filling pressure relation documents increased left ventricular function in Group II and reduced function in the Group III. Changes in contractility might account for these differences.

Myocardial contractility and wall stress: Circumferential fiber shortening rate V_{cf} has been proposed by several investigators as a reliable index of left ventricular performance, which reflects the inotropic state of the myocardium.[14,15] The similarity of V_{cf} in Group I and the control subjects and the divergent variation from normal in Groups II and III would indicate that contractility is normal in Group I, augmented in Group II and reduced in Group III. However, before this interpretation is accepted, influence of cardiac load on V_{cf} should be considered. It has been documented that V_{cf} is affected minimally by changes in preload but responds inversely to changes in afterload,[16] so that afterload variations may, at times, limit clinical applicability of V_{cf} for assessment of contractility. Whenever a low value of V_{cf} is observed in a patient with increased afterload (left ventricular wall stress), the question may arise of whether this value reflects a reduced inotropic state of the myocardium or simply a shift (due to the increased wall stress) to a different point in a normal stress-velocity curve. From an analysis of Figure 3 a relation seems to exist in Group III between the depressed V_{cf} and the elevated impedance to ejection (systemic vascular resistance) and wall stress; the same relation is not evident in Group II, in which enhanced V_{cf} was associated with normal wall stress and increased systemic vascular resistance. However, when related to the velocity of fiber shortening, the value of circumferential wall stress (as it was calculated in this study) is limited because it reflects ventricular load of the earlier part of the systole when fiber shortening does not occur. For this purpose, V_{cf} and wall stress should be obtained throughout the ejection phase; this requires high fidelity intraventricular pressure recordings simultaneous with continuous measurements of ventricular internal diameter and wall thickness. These measurements are not easily derived, particularly without the aid of a computer. Therefore, the question of whether the improvement of V_{cf} in Group II and its reduction in Group III depend on opposite variations from normal in myocardial contractility or in wall stress during ejection remains basically unanswered.

Right ventricular function: Findings in the right side of the heart offer some further considerations. In both Groups II and III the functional pattern of the right ventricle, as evaluated by the mean rate of systolic ejection (Fig. 2) and the stroke index-filling pressure relation (Fig. 3), was similar to that of the left ventricle. The improved right ventricular function in Group II and the depressed function in Group III can hardly be explained in terms of afterload, but can be better explained in terms of changes in the contractile state that involve both sides of the heart.[17]

As mentioned in the introduction, earlier reports[1–3] on hypertensive heart disease indicated that left ventricular function is impaired in the presence of hypertrophy. A more recent assessment by Dunn et al.[18] provided the same evidence. Our present findings in agreement with those reported by Karliner et al.,[19] lead to different conclusions. The discrepancy probably results from the substantial difference between present and earlier criteria (classification based on electrocardiographic and roentgenographic data)[1–3,18] used to define the structural characteristics of the left ventricle.

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Renin, Aldosterone and Cardiac Decompensation: Studies With an Oral Converting Enzyme Inhibitor in Heart Failure

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Congestive heart failure is frequently associated with stimulation of the renin-angiotensin system; the resulting increase in peripheral resistance and secondary aldosteronism, in turn, adds to the cardiac load and thus helps perpetuate decompensation. An oral converting enzyme inhibitor (captopril) was therefore tried in six normotensive patients with heart failure resistant to digitalis, diuretic agents and vasodilator therapy. After an oral dose of 25 to 50 mg, cardiac output and stroke volume increased ($P < 0.01$ for both) whereas mean arterial pressure, total peripheral resistance and pulmonary capillary wedge pressure were significantly reduced ($P < 0.05$). The increase in flow correlated closely with the reduction in mean arterial pressure ($r = 0.94$; $P < 0.001$) and in pulmonary capillary wedge pressure ($r = 0.87$; $P < 0.01$). These effects were maximal within 90 minutes and lasted an average of 4 hours. There was no significant correlation between pretreatment plasma renin activity and a decrease in either mean arterial pressure or total peripheral resistance ($r = 0.21$ and -0.41, respectively; $P > 0.10$ for both).

Continued follow-up study for 1 month showed a gradual improvement manifested by an increased effort tolerance and a reduction in body weight from 71.9 ± 8.4 kg (mean ± standard error of the mean) to 68.5 ± 9.0 kg ($P < 0.05$). Both total peripheral resistance and mean pulmonary transit time were reduced significantly ($P < 0.05$) but changes in cardiac output and stroke volume were minor. Plasma renin activity increased in all but one patient whereas the plasma aldosterone level was reduced in all in close correlation with its pretreatment level ($r = -0.971$; $P < 0.001$). The results suggest that treatment with captopril could be helpful in heart failure by reducing both peripheral resistance and plasma aldosterone levels.

Disturbances induced by cardiac decompensation are not limited to the hemodynamic effects of a reduced pumping ability. Particularly important among the compensatory mechanisms mobilized in heart failure are stimulation of the adrenergic system[1,2] and development of secondary aldosteronism.[3] The two systems are closely interrelated because sympathetic stimulation leads to renin release[4] and sodium retention potentiates the vascular effects of norepinephrine.[5] Although stimulation of such powerful systems undoubtedly helps restore homeostasis, it may sometimes cause them to overshoot their mark and contribute to the signs, symptoms and complications of heart failure.

In contrast to the relatively homogeneous picture obtained from studies of the autonomic nervous system in heart failure,[1,2,6] determinations of plasma renin activity in cardiac decompensation reveal a wide scatter of patterns.[7–9] Furthermore, the relation of aldosterone to heart failure has still not been fully elucidated,[3,7,10–12] possibly because of differences between cardiac failure in man and that in experimental animal models and also because of the unavoidable heterogeneity of cases as well as the influence of therapy, dietary restrictions and timing of studies in relation to the course of decompensation.[7,13] Not only can

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multiple factors influence plasma renin activity, aldosterone levels and plasma volume in heart failure, but also, as pointed out by Watkins et al.,[13] some disturbances consequent to cardiac decompensation may have simultaneously opposite effects on renin release. Thus, systemic arterial hypotension tends to stimulate renin release[14] whereas left atrial or systemic venous congestion reflexly reduces it.[15–17] Apart from this complexity is the added difficulty of extrapolating the results of renin studies in animals to hypertensive conditions[18] or heart failure in human beings.[13]

Recent pharmacologic advances have added a new practical dimension to these problems. Drugs that interfere specifically with various steps in the renin-aldosterone cascade have been used to study or to treat various types of heart failure.[9,13,19,20] This approach can have a dual advantage: (1) It can help estimate the pathophysiologic significance of circulating hormonal levels, and (2) it can assist in evaluating therapeutic possibilities for resistant heart failure. The latter might not be restricted to control of emergency conditions only; with the development of captopril by Ondetti et al.,[21] long-term treatment of heart failure by converting enzyme inhibition became a possibility. Captopril reduced total peripheral resistance without significantly increasing cardiac output or heart rate[22] and normalized elevated plasma aldosterone levels in hypertensive patients.[23] Therefore, it appeared possible that benefit might be derived in patients with heart failure even when cardiac decompensation was not due to or exacerbated by hypertension. This report describes our experience with six normotensive patients with heart failure that was resistant to intensive conventional treatment and that necessitated frequent hospitalization of the patient.

Methods

Protocol of Studies

Patients: Six patients (Table I) were referred for treatment with captopril because of heart failure resistant to optimal treatment with rest, digitalis, diuretic agents, rest and prazosin; none had an operable cause for the decompensation or evidence of valve obstruction. All patients gave their free informed consent to the trial and tests, which had also been approved by the Institutional Review Committee.

Hemodynamic studies: In addition to careful and close clinical follow-up study, special investigations included repeated hemodynamic evaluations both by invasive methods (thermodilution or indocyanine green dye-dilution) and by radionuclide (technetium-99 human serum albumin) determination of cardiac output, mean transit time and cardiopulmonary volume.[24] The methods used as well as their close correlation have previously been described in detail.[22,24,25] Studies were performed at regular intervals, the first, 1 day before the administration of captopril (radionuclide method); on the day therapy was initiated, cardiac output was determined invasively immediately before the first dose and thereafter at half hour intervals until a return to baseline values. Hemodynamic studies by radionuclides were again performed after 1 week and after 1 month of continued treatment. The same technique was used consistently in each patient; the acute effects reported are based on intraarterial determination of pressure with dye-dilution or thermodilution measurement of cardiac output. The long-term results in all are based on radionuclide determination of output with indirect recording of blood pressure; the latter had been shown in the initial sutdy in each patient to correlate closely with intraarterial records.

Treatment protocol: Throughout the study all patients were maintained on their previous regimen of digitalis and diuretic agents; only vasodilator therapy was discontinued at least 5 to 10 days before. The trial began with a period of rest for at least 1 week in the hospital, after which control determinations were obtained. Treatment began with one dose of 25 mg of captopril (except for the first patient who was given 12.5 mg the first day and 25 mg the next day). If an adequate hemodynamic response was obtained, treatment was continued with 25 mg three times a day; if not, a dose of 50 mg was given the next morning, the same hemodynamic determinations were obtained, and treatment was continued with 50 mg three times a day. Throughout the follow-up period, digitalis and diuretic dosage was maintained constant. The first day (invasive) study was performed in only five patients because technical difficulties prevented insertion of the catheter in the sixth patient. Long-term studies were performed in all six patients.

Methodology

The methods used have previously been described in detail.[22–25] Plasma volume, renin activity and aldosterone levels were determined the morning after an overnight fast and at least 30 minutes of supine rest. Plasma renin activity was determined by radioimmunoassay and expressed in nanograms per milliliter per hour (ng/ml per hour).[26] Plasma volume was determined by ^{125}I human serum albumin using a 10 minute equilibration period, and blood volume was calculated from plasma volume and simultaneously measured hematocrit; results were expressed in milliliters per centimeter (ml/cm).[27] The plasma aldosterone level was determined by radioimmunoassay and expressed in nanograms per deciliter (ng/dl); normal values for our laboratory range from 3.0 to 10.0 ng/dl.[23] Cardiac output was determined by dilution methods (thermal, dye or radionuclide) using the Stewart-Hamilton formula.[28] Blood pressure was determined intraarterially during the 1st day of drug administration and by auscultation on other occasions; the results of the two methods were shown during the invasive study to agree closely. Heart rate during the hemodynamic studies was determined from continuous recording of the lead II electrocardiogram. Hemodynamic indexes were calculated by standard formulas.[22,25]

TABLE 1

Clinical Data on Six Patients Treated With Captopril

Case no.	Age (yr) & Sex	Diagnosis	Functional Class	PRA (ng/dl)	Duration of Heart Failure
1	61 M	Coronary heart disease, remote myocardial infarct	III/IV	2.6	6.5 yr
2	57 M	Myocarditis	III	4.3	9 mo
3	63 M	Coronary heart disease, mitral valve replacement	IV	9.0	10.5 mo
4	75 F	Myocarditis	IV	2.5	3 yr
5	34 M	Myocarditis	III	6.4	3.3 yr
6	69 M	Coronary heart disease, aortic valve replacement	IV	15.6	14 mo

PRA = plasma renin activity.

Statistical analysis: Each patient served as his own control and statistical significance of the results were determined by the paired t test. Correlation coefficients and tests of significance were calculated by standard statistical methods[29]; values were reported as average ± standard error of the mean.

Results

Acute effects of a single dose of captopril: The maximal effect of a single oral dose (25 mg in three patients and 50 mg in two patients) occurred from 1 to 2 hours after ingestion; the maximal reduction in pulmonary wedge pressure occurred 90 minutes after administration of the dose in four patients and two hours after in the fifth. Similarly, the maximal reduction in mean arterial pressure was recorded 90 minutes after captopril in four patients and at 60 minutes after the drug in one. Hemodynamic indexes returned to control levels within 5 hours. The values to be reported are, therefore, those recorded 1.5 hours after 25 to 50 mg of captopril given orally.

A significant reduction occurred in the following indexes: mean arterial pressure (−18.4 ± 3.3 mm Hg [standard error of the difference]; $P < 0.001$), heart rate (−7 ± 20.5 beats/min; $P < 0.02$), total peripheral resistance (−13.8 ± 2.35 units; $P < 0.001$) and pulmonary wedge pressure (−11.9 ± 2.88 mm Hg; $P < 0.005$). Simultaneously, stroke volume increased by 15.6 ± 2.9 ml ($P < 0.001$) and cardiac output by 0.82 ± 0.27 liters/min ($P < 0.02$). The variations in cardiac output recorded at half-hour intervals during the 5 hour period of observation after the oral dose of captopril correlated significantly with simultaneous changes in both pulmonary wedge pressure ($r = -0.711$; $P < 0.05$) and mean arterial pressure ($r = -0.839$; $P < 0.01$). Similar correlations with even higher coefficients (r values) were also found between changes in stroke volume and variations in both pulmonary wedge and mean systemic pressure during the same period ($r = -0.831$, $P < 0.01$; and $r = -0.980$ $P < 0.001$, respectively) (Fig. 1).

Control plasma renin activity varied from normal to significantly elevated (range 2.6 to 15.6 ng/ml) (Table I); none of the six patients had low levels of plasma renin activity. No statistically significant correlation was found between pretreatment plasma renin activity and reduction of either mean arterial pressure ($r = 0.21$ [not significant]) or peripheral resistance ($r = -0.41$; $P > 0.10$); however, the lack of significance could be due to the small number of patients studied.

Long-term effects of continued therapy: Clinical improvement as evidenced by fewer symptoms, loss of weight and greater capacity for exercise was definite in five patients; in the sixth, changes were equivocal. Body weight before the administration of captopril averaged 71.19 ± 8.4 kg; after 1 month of treatment it was reduced to 68.5 ± 9.0 kg ($P < 0.05$), presumably because of loss of fluid as evidenced by the disappearance or marked reduction in edema. Exercise capacity (bicycle ergometer) was tested in five patients (the sixth patient was incapacitated by chronic arthritis) by physicians not involved in the study. The level achieved and the duration of exercise were improved in four and unchanged in one. Hemodynamic effects of maintained therapy were less impressive than the acute changes already described in the first few hours of the initial dose. Long-term changes in various indexes continued in the same direction as the early effects, namely, mean arterial pressure as well as total peripheral resistance were reduced with a simultaneous increase in stroke volume (Fig. 2). Cardiopulmonary blood volume was lower than the control value, both at 1 week and at 1

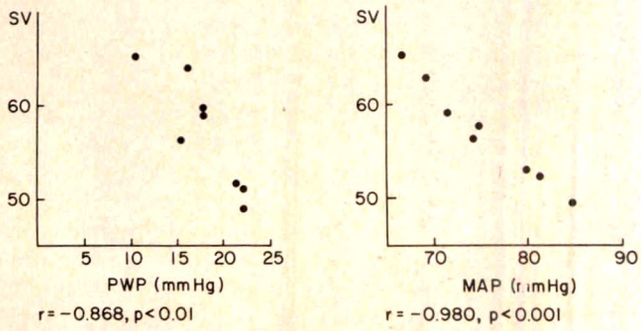

FIGURE 1. Acute effects of captopril. Changes in stroke volume (SV), pulmonary wedge pressure (PWP) and mean arterial pressure (MAP) determined at 30 to 60 minute intervals for 5 hours after the oral administration of captopril (25 mg). Each point represents the average value of five patients.

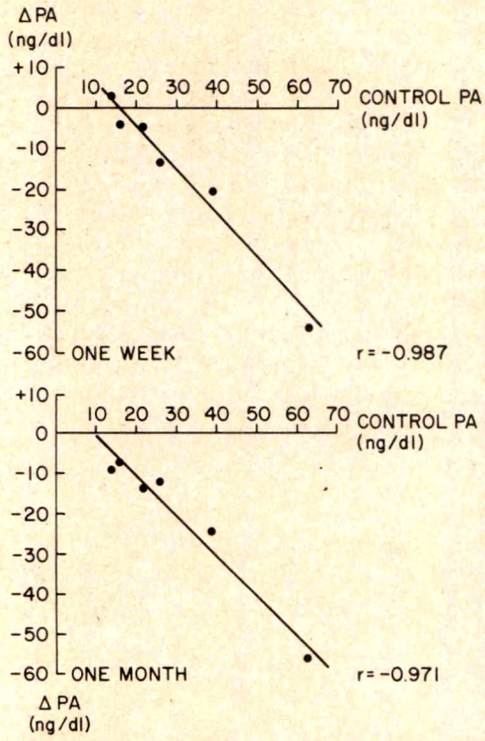

FIGURE 2. Changes in stroke volume (SV), cardiac output (CO), cardiopulmonary volume (CPV) and calculated total peripheral resistance (TPR) observed in six patients during 1 month of therapy with captopril. Sequential determinations were obtained in all patients before addition of converting enzyme inhibitor (C) and then after 1 week (W_1) and 1 month (M_1) of continued therapy; digitalis and diuretic dosages were unchanged throughout the study period. L = liters; p = probability. **Asterisks** indicate significant changes.

month of treatment (1,086 and 914 ml, respectively versus 1,200 ml before treatment); however, only the latter change (after 1 month of treatment) was of statistical significance (−286 ± 97.6 ml [standard error of the difference]; $P < 0.05$). The most consistent change was a shortening in mean transit time from 20.2 to 14.3 seconds after 1 month of treatment ($P < 0.02$). Concomitantly, the ratio of cardiopulmonary to total blood volume decreased from 24.9 to 18.9 percent (standard error of the difference 1.96) ($P < 0.05$).

Plasma renin activity tended to increase with treatment (from 6.73 ± 2.04 ng/ml to 19.1 ± 11.5 and 19.07 ± 8.9 ng/ml at 1 week and 1 month, respectively) but changes were not consistent in all and the results did not attain statistical significance. In contrast, plasma aldosterone levels decreased early during therapy and were maintained lower than the control value (9.8 ± 1.8 versus 30.1 ± 7.5 ng/dl; $P < 0.02$); the reduction in plasma aldosterone levels correlated significantly with pretreatment levels, $r = -0.987$ for results after 1 week of therapy and $r = -0.971$ after 1 month ($P < 0.001$ for both) (Fig. 3). A plasma aldosterone level below 5.0 ng/dl was not recorded in any patient during the entire period of treatment; the lowest value was 5.2 ng/dl, which is within the normal range for our laboratory and therefore not indicative of hypoaldosteronism.

Discussion

Added to a continued regimen of digitalis and diuretic agents, the oral converting enzyme inhibitor (captopril) helped to improve cardiac compensation and to prevent recurrent episodes of heart failure in five of six patients in whom it was tried. All were patients with long-standing heart failure who had to be hospitalized repeatedly because of shortness of breath with minimal activity, fatigue and dependent edema. The improvement was produced over a period of weeks, which might have been due to our conservative approach. The doses given were 25 to 50 mg three times a day rather than the maximal allowed dosage of 300 to 450 mg daily.

Hemodynamic effects versus clinical improvement: Evaluation of the response to captopril revealed two noteworthy features: (1) an apparent dichotomy between hemodynamic effects and clinical improvement, and (2) a marked reduction in plasma aldosterone levels. Peak increases in cardiac output and stroke volume as well as reductions in pulmonary wedge pressure and total peripheral resistance occurred within 2 hours of oral administration of captopril. The hemodynamic pattern of response was that expected from vasodilator therapy in cardiac insufficiency[9,30–32]; changes in cardiac output and stroke volume during the first period of observation correlated inversely ($P < 0.001$) with variations in pulmonary wedge and mean systemic arterial pressures (Fig. 1). No increase in heart rate occurred despite the reduction in mean arterial pressure, a finding reported previously in patients with heart failure who were given nitroprusside.[30] In addition to general factors blunting heart rate responses to vasodilators in cardiac decompensation,[31] there may be in our patients a special effect resulting from interference with the renin-angiotensin system. Reduction of arterial pressure by either angiotensin antagonists[22,33,34] or converting enzyme inhibitors[9,23,35] did not produce the significant tachycardia noted in hypertensive patients. This factor was tentatively related to blunting of baroreceptor sensitivity[36] or alterations in parasympathetic activity,[37] but the responsible mechanisms have not yet been satisfactorily determined.

Despite these hemodynamic effects, the patients did not show an impressive functional improvement at that time. The lack of an obvious relation with the patients' clinical status might in part be due to their chronic cardiac condition; because they did not have acute failure at the time of treatment the hemodynamic improvement was not translated into relief from urgent symptoms. In contrast, after 1 month of therapy, although the patients obviously felt better, the long-term hemodynamic effects were less pronounced than the early changes, some barely reaching statistical significance (Fig. 2). However, these effects were in the same direction as the acute changes, and the lack of statistical significance might in part be due to the small number of patients involved.

Reductions in peripheral resistance: The most consistent feature was the reduction in total peripheral resistance, which was found in the studies performed 1 week and 1 month after the start of therapy (Fig. 2). However, there was little change in cardiac output at either time and the increase in stroke volume, although impressive in some patients, did not achieve consistently statistical significance for the whole group. Mean transit time and cardiopulmonary volume were gradually reduced over 1 month of treatment from control values of 20.2 ± 2.9 seconds and 1,200 ± 160 ml to 14.3 ± 2.5 seconds and 914 ± 95 ml, respectively ($P < 0.05$). The reduction in cardiopulmonary volume might in part be related to systemic venodilation and peripheral relocation of intravascular volume[25] as suggested by the concurrent reduction in the cardiopulmonary volume to total body volume ratio from 25 to 19 percent ($P < 0.05$).

Although cardiac output in most patients did not change appreciably, after 1 month of maintained therapy the patients showed obvious improvement with

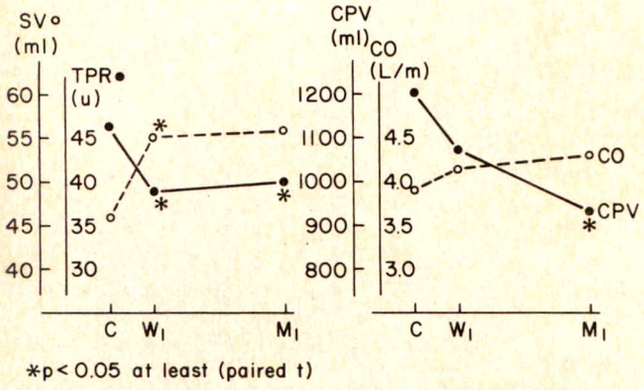

FIGURE 3. Reduction in plasma aldosterone (PA) during captopril therapy closely correlated with pretreatment levels; the same high correlation coefficient (r) was found after 1 week and after 1 month of continued treatment ($P < 0.01$ for both).

better exercise tolerance, return of liver size to normal and diminution or disappearance of dependent edema. The reduction in arterial pressure observed after the first dose of captopril (from 84.6 to 66.2 mm Hg; $P < 0.001$) was not sustained with long-term treatment; by the 1st week arterial pressure was only 8 mm Hg below control (difference not significant) and after 1 month it was close to pretreatment levels (−4 mm Hg, [not significant]). Orthostatic hypotension was not a problem in these five patients despite diuretic therapy and moderate salt restriction. We have had the same experience with captopril in hypertensive patients.[23]

Reduction in plasma aldosterone and interference in renin-angiotensin system: It is tempting to relate the gradual improvement in cardiac decompensation to the combined effect of a sustained reduction in peripheral resistance with a decrease in the plasma aldosterone levels. In contrast to plasma renin activity, which was elevated in some patients and unchanged in others, the plasma aldosterone level was consistently reduced by captopril; the magnitude of this reduction correlated closely with pretreatment aldosterone levels ($r = -0.987$ and -0.971 at 1 week and 1 month of treatment, respectively) (Fig. 3). We[23] found the same correlation during treatment of compensated hypertensive patients with the same converting enzyme inhibitor, suggesting that the reduction in plasma aldosterone was related at least in part to interference with the formation of angiotensin II. Improved cardiac function could also help decrease the aldosterone level by improving its metabolic clearance rate.[38] To the extent that secondary aldosteronism, by leading to sodium retention, contributes to the persistence of heart failure and the resistance to therapy,[3] normalization of aldosterone levels may be a significant factor in the beneficial long-term effect of converting enzyme inhibition. In that respect, the increase in creatine clearance and sodium excretion, which was recently reported with an intravenous converting enzyme inhibitor (teprotide),[39] might suggest yet another reason for the therapeutic effect of this approach. Angiotensin-mediated renal vasoconstriction was thought to be a possible cause of the reduction in renal blood flow typically found in cardiac failure.[7] If the reduction in plasma aldosterone levels is an index of continued interference by captopril in the production of angiotensin II, that interference with the renin-angiotensin cascade would be an added factor in reducing renal vasoconstriction and in enhancing sodium excretion. In patients on digitalis and diuretic therapy, control of aldosteronism may have the added advantage of preventing hypokalemia. However, the possible risk of hyperkalemia must be recognized especially when diuretic therapy is discontinued. Potassium levels increased transiently to 5.5 mEq/liter in two patients; in a third, serum potassium levels increased to 6.0 mEq/liter after diuretic therapy had been discontinued because of the marked improvement in the patient's condition.

Although the control of secondary aldosteronism could be ascribed to converting enzyme inhibition,[13,23] it is impossible to assume that the reduction in total peripheral resistance was unequivocally due to interference with angiotensin II formation. Turini et al.[9] and Gavras et al.[20] suggested that activation of the renin-angiotensin system could be responsible in part for the increased peripheral resistance found in most cases of heart failure. However, the reduction of peripheral resistance by converting enzyme inhibition, although suggestive, cannot be construed as definite evidence of that possibility. Many investigators do not believe that the long-term reduction of blood pressure and peripheral resistance by captopril is related solely to interference with angiotensin production, but this remains a controversial subject.[23,40–42] Whatever the case may be, the hemodynamic effects of captopril in heart failure might have as complex a mechanism as its antihypertensive action.

The role of neurohumoral factors in cardiac decompensation has acquired particular importance because of our ability to influence these factors with therapy. This study and others[9,19,20] have described early beneficial effects of interference with the renin system; beta receptor blockade was recently reported to improve survival in patients with congestive cardiomyopathy.[43] However, to the extent that adrenergic stimulation and secondary aldosteronism are compensatory mechanisms, their blockade could be a double-edged sword, as demonstrated by the deleterious effect of guanethidine in valvular heart disease and of propranolol in heart failure.[6] Longer-term studies as well as careful individual evaluations are needed to determine the precise indications for this approach.

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Role of Vasoconstrictor Mechanisms in the Control of Left Ventricular Performance of the Normal and Damaged Heart

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The effect on the left ventricle of changes in the state of the arterial vasculature is best identified by utilizing calculations of pulsatile rather than steady flow phenomena. Impedance is the most satisfactory term to describe this effect. The normal ventricle compensates for changes in impedance largely by changes in preload, but the damaged heart loses this compensatory ability and its stroke volume becomes inversely related to outflow resistance. Patients with heart failure behave in a similar fashion and pharmacologic vasodilation may induce marked improvement in left ventricular pump function. Inappropriate vasoconstriction in heart failure may result from stimulation of the sympathetic or renin-angiotensin system. Early experience with converting enzyme inhibitors suggests that blockade of the formation of angiotensin II may be a useful means of treating some patients with heart failure.

The functional state of the peripheral circulation is vital not only as a determinant of arterial pressure but also as an important factor in the control of left ventricular pump performance. Despite this pivotal role of the arterial bed, analysis of how it impedes left ventricular ejection and contributes to arterial pressure has not received adequate attention.

Assessment of Peripheral Vascular Bed Impedance

It is customary in hemodynamic assessment to calculate the peripheral vascular resistance as the ratio of mean pressure to mean flow. Indeed, this calculated resistance is often viewed as an adequate means of characterizing the functional state of the systemic vascular bed. In a pulsatile system, however, mean pressure and mean flow are contrived values that have little reality. Systolic and diastolic arterial pressure are determined by a complex interaction of phenomena involving compliance and resistance of the vascular bed, inertia and viscosity of the blood and the dynamics of left ventricular ejection. It is clear that mean resistance may provide a misleading index of the determinants of arterial pressure or of the stress placed on the left ventricle by the peripheral arterial bed. The term "afterload" is often applied to this pressure load placed on the left ventricle, but this term has its origin in isolated muscle mechanics and refers to wall stress placed on the left ventricle during ejection.[1] Afterload thus is dependent on ventricular chamber size as well as pressure and stroke volume and is not a useful means of assessing the independent contribution of the periphery.

Impedance is a more satisfactory term, because it assesses the sum of all factors that exert resistance to the instantaneous movement of blood beyond the aortic valve during systole. These factors are: (1)

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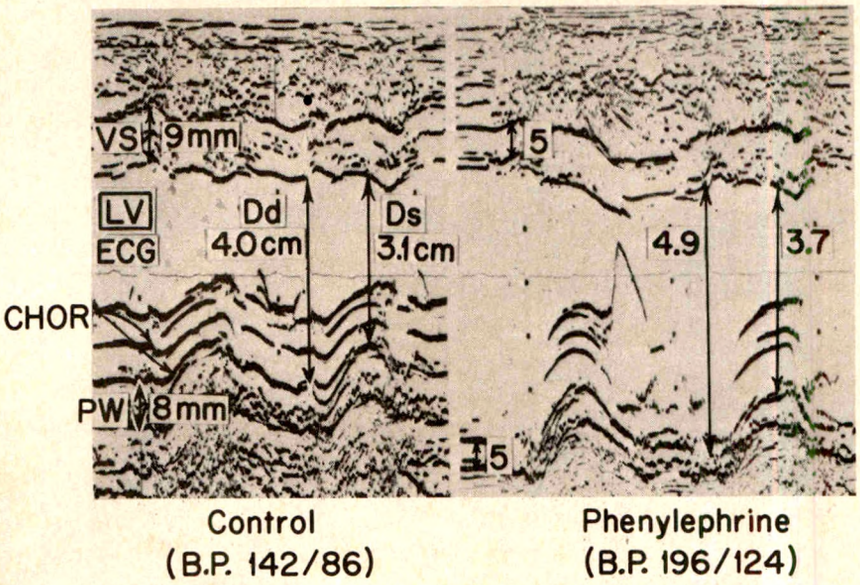

FIGURE 1. Effect of phenylephrine on left ventricular (LV) chamber size assessed with M mode echocardiography in an awake dog. The increase in arterial blood pressure (B.P.) is associated with an increase in end-systolic diameter (Ds) from 3.1 to 3.7 cm, but a concomitant increase in end-diastolic diameter (Dd) from 4.0 to 4.9 cm prevents a decline in stroke volume. CHOR = chordae tendineae; ECG = electrocardiogram; IVS = interventricular septum; PW = posterior left ventricular wall.

compliance of the large arteries, (2) radius of the small arteries, (3) small vessel compliance, (4) inertia and (5) blood viscosity. The problem with impedance is that its measurement is difficult and its interpretation complicated. Analysis in the frequency domain, the usual approach, requires Fourier analysis of high fidelity pressure and flow signals from the same site in the aorta.[2] A time domain method also has been employed utilizing analysis of the diastolic portion of a central or peripheral arterial pulse wave.[3] Further study of the effects of aging, disease and drug therapy on the peripheral circulation applying these techniques is urgently needed before the intricate interrelation between the left ventricle and the arterial circulation can be understood.

Role of Aortic Impedance in Left Ventricular Performance

Normal left ventricle: The response of the normal left ventricle to a change in aortic inflow impedance is still controversial. In their elegant studies in the 1960's, Sarnoff et al.[4] demonstrated that the stroke volume of the left ventricle remains constant as aortic resistance is acutely altered. They termed this phenomenon "homeometric autoregulation," thus implying that the ventricle is able to adjust its stroke work without a change in end-diastolic size when called on to generate more or less pressure. Although this response in their experimental model may have been at least in part due to an intrinsic change in muscle function, under more physiologic conditions the adjustment in stroke volume appears to be due largely to a change in end-diastolic fiber length.

When awake dogs were subjected to drug infusions to acutely vasoconstrict or vasodilate the arterial bed, adjustments to maintain stroke volume seemed to be dependent on preload changes. In Figure 1 the left ventricular dimensional change in response to an infusion of phenylephrine is shown. Echocardiography was utilized with the probe positioned on the right side of the chest, as previously described by our laboratory.[5] During the vasoconstrictor effect of phenylephrine left ventricular end-systolic diameter was increased, a reflection of increased aortic impedance. However, stroke volume was maintained by a concomitant increase in end-diastolic diameter. Even when cardiac slowing in response to the induced hypertension was prevented by pacing, the end-diastolic diameter increased and stroke volume remained constant as a result of what may be interpreted as a Frank-Starling mechanism. Similarly, a vasodilator stimulus results in a reduced end-systolic diameter by virtue of a lowered aortic impedance. This response can be noted even in the presence of an inotropic stimulus (Fig. 2). However, an increase in stroke volume is not observed, because the end-diastolic diameter is concomitantly reduced. Thus, ejection fraction of the normal left ventricle is very dependent on aortic impedance but stroke volume is importantly modified by preload changes. Nevertheless, because these studies only assessed acute responses, the possibility of a delayed adjustment to changes in impedance not dependent on preload cannot be ruled out.

Diseased left ventricle: The situation in the normal heart may be altered by disease. We have studied the effect of acute damage to the left ventricle on the response of the dog to a similar arterial vasoconstrictor and vasodilator stimulus. The left ventricle was damaged by repetitive direct current shock applied across the left ventricle in anesthetized closed chest dogs.[6] Whereas changes in systemic vascular resistance induced in normal dogs were associated with an unchanged stroke volume, 2 hours after left ventricular damage the stroke volume became inversely related to vascular resistance. Because these dogs also showed a depressed cardiac output response to a volume load it is likely that the emergence of a stroke volume depen-

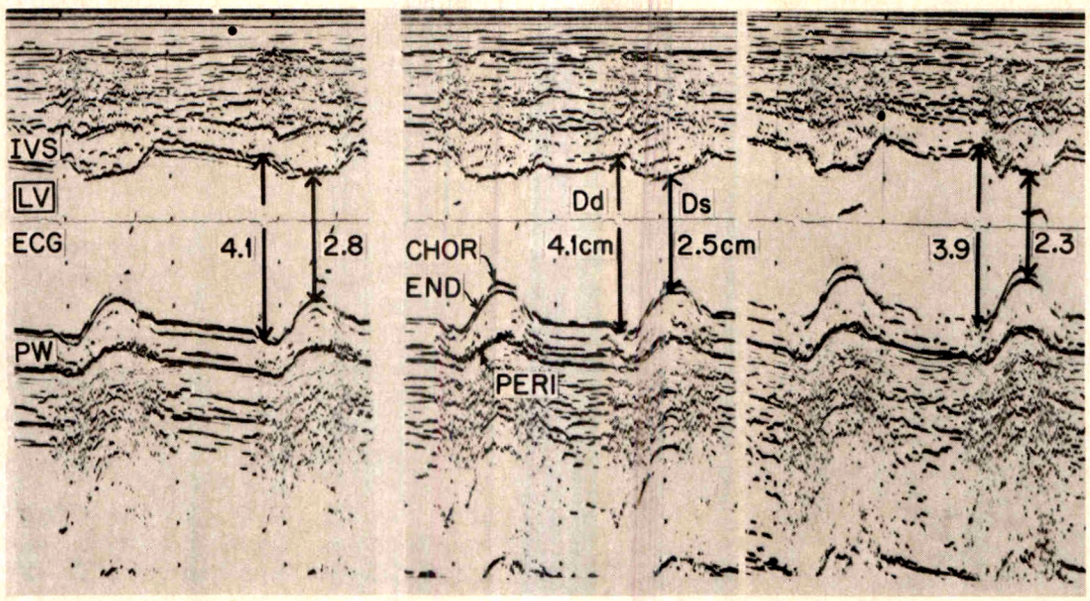

FIGURE 2. Echocardiographic response to infusion of sodium nitroprusside superimposed on an inotropic stimulus from dopamine in an awake dog. Note that nitroprusside further reduces end-systolic diameter (Ds) of the left ventricle (LV) but a concomitant reduction of end-diastolic diameter (Dd) from 4.1 to 3.9 cm prevents stroke volume from rising. END = endocardial suface; PERI = pericardial surface of posterior wall (PW). Unidentified abbreviations as in Figure 1.

dence on aortic impedance can be attributed at least in part to loss of a brisk Frank-Starling mechanism to counteract the normal influence of impedance on ejection fraction.

Clinical applications in hypertension and heart failure: These observations on the role of aortic impedance in the control of left ventricular performance may have important implications in our understanding of the natural history of experimental and clinical hypertension and of heart failure. In hypertension the adverse effect of a high impedance on left ventricular performance may not become apparent until left ventricular damage supervenes either because of progressive hypertrophy or collagen growth, or both, or because of inadequacy of coronary perfusion. However, in primary disease of the left ventricle, an inappropriately increased aortic impedance may be an early factor in pump dysfunction.[7]

Drugs to reduce aortic impedance: Observations made during the past few years on patients with heart failure have clearly demonstrated the salutary effect on left ventricular performance of drugs that reduce aortic impedance.[8] These initial therapeutic efforts employed pharmacologic agents that have a nonspecific vasodilator effect.[8–10] However, the inappropriately increased aortic impedance in heart failure could result from neurohumoral mechanisms that would be responsive to more specific therapy. In a group of hospitalized patients with severe heart failure being treated with digitalis and diuretic drugs, plasma norepinephrine levels were consistently increased and plasma renin activity was frequently but not always elevated (Table I). If these increased levels reflect a role for the sympathetic nervous system and the renin-angiotensin system in maintenance of a high aortic impedance, then therapy directed at these mechanisms could have a uniquely beneficial effect.

The wide range of values noted for plasma renin activity from low to exceedingly high levels suggests that renin is not stimulated uniformly in patients with heart failure. The reasons for this variation in the degree of renin-angiotensin stimulation was not apparent from an examination of clinical severity, hemodynamic measurements or results of therapy.[11] We have noted, however, that plasma renin activity is elevated in hyponatremic subjects and that it is inversely correlated with serum sodium concentration.[11] Regardless of the mechanism of renin stimulation angiotensin could well

TABLE I

Resting Plasma Norepinephrine (NE) and Renin Activity (PRA) in Congestive Heart Failure (CHF)

Subjects	NE (pg/ml)	PRA (ng/ml per hr)
Normal (no. = 10)		
Mean	204.5	1.8
SEM	±26.4	±0.3
Congestive heart failure (no. = 23)		
Mean	682.5	13.6
SEM	±80.4	±3.1
P	<0.001	<0.025

P = probability; SEM = standard error of the mean.

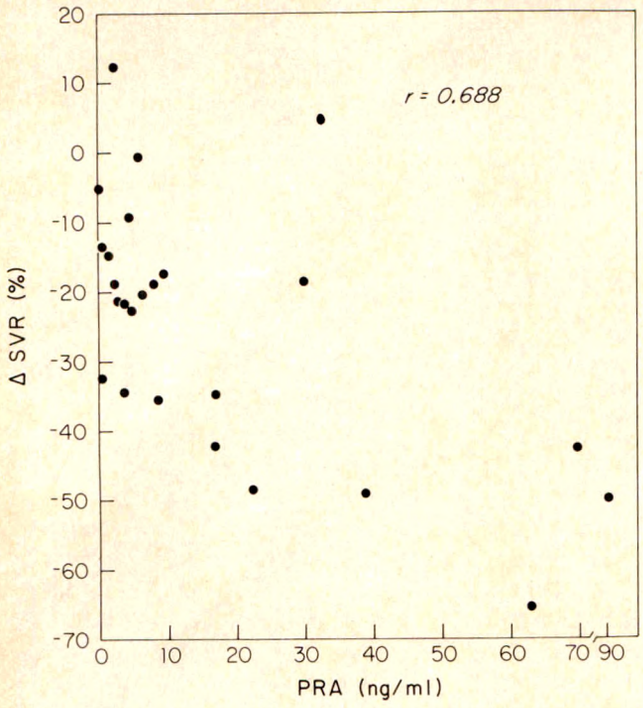

FIGURE 3. Relation between control resting supine plasma renin activity (PRA) in ng/ml per hour and percent change in systemic vascular resistance (SVR) in response to intravenous administration of the converting enzyme inhibitors teprotide (SQ 20, 881) or oral administration of captopril (SQ 14, 225) in 24 patients with moderate to severe congestive heart failure. r = correlation coefficient.

play a role in the increased aortic impedance in at least some patients with heart failure.

The converting enzyme inhibitors: These agents offer a useful although unfortunately not specific means of assessing the influence of angiotensin on the circulation. Both teprotide (SQ 20, 881), an intravenous natural peptide, and captopril (SQ 14, 225), an orally effective synthetic agent, exert a vasodilator effect in patients with heart failure.[12,13] The magnitude of the hemodynamic response in patients with heart failure bears some relationship to the control plasma renin activity (Fig. 3), but apparently other factors are operative as well. Whether the nonrenin-related component of the response is related to inhibited degradation of bradykinin or to other effects of converting enzyme inhibition is not known.

Preliminary observations with chronic administration of captopril in patients with severe heart failure indicate that the hemodynamic response is maintained and that clinical improvement occurs. In these studies patients have exhibited increased exercise tolerance and reduction in symptoms of fatigue and shortness of breath during therapy of 3 to 6 months' duration. Whether the response to this specific vasodilator intervention will prove to be better than that to the nonspecific vasodilator drugs remains to be seen. In particular, studies analyzing the regional blood flow responses to these therapeutic agents are needed to assess their relative efficacy in restoring normal circulatory function.

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Effects of Cardiac Hypertrophy Secondary to Hypertension on the Coronary Circulation

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For many years clinicians have suspected that hypertrophied ventricles have an inadequate coronary circulation. Recent studies have confirmed early observations that flow per gram in hypertrophied ventricles is normal at rest. However, coronary vascular resistance is greatly increased when hypertension is the cause of left ventricular hypertrophy. Studies that have employed labeled microspheres to assess regional myocardial perfusion have shown that the transmural distribution of myocardial perfusion is often abnormal in dogs with left ventricular hypertrophy. In addition, studies of cardiac hypertrophy in many animal models have shown that maximal coronary vasodilatation is limited substantially. Furthermore, when hypertrophied hearts are subjected to a physiologic stress that induces coronary vasodilatation, endocardial underperfusion occurs frequently. Thus, studies in animals suggest that cardiac hypertrophy adversely affects the coronary circulation. The availability of new techniques for estimating phasic and transmural coronary blood flow in man should make it possible to extend these studies to patients with cardiac hypertrophy.

Clinicians for many years have postulated that the coronary circulation becomes inadequate when substantial cardiac hypertrophy occurs. This hypothesis was initially based on two clinical observations: (1) Many patients with left ventricular hypertrophy have angina pectoris even when no coronary lesions are present,[1] and (2) electrocardiographic abnormalities suggestive of ischemia occur frequently at rest and during exercise in patients with left ventricular hypertrophy.[1,2] Subsequently, pathologists noted that subendocardial fibrosis is common in hypertrophied ventricles and postulated that fibrosis resulted from "coronary insufficiency."[3] More detailed anatomic studies demonstrated that the number of coronary collateral vessels in hypertrophied hearts is increased,[4] the capillary density is decreased by 20 to 30 percent in hearts with pressure-induced cardiac hypertrophy[5,6] and the decrease in capillary density is most prominent in the inner third of the hypertrophied ventricle.[7] Thus, by 1975, data from several disciplines suggested that the coronary circulation may be inadequate in hypertrophied hearts.

Early physiologic studies did not reveal any abnormalities in coronary blood flow in animals or in patients with cardiac hypertrophy.[8–12] In these studies, regional myocardial blood flow was not measured and most measurements of coronary blood flow were obtained at rest. At least two mechanisms could contribute to inadequate myocardial perfusion in the hypertrophied heart: (1) associated hemodynamic alterations related to the cause of the hypertrophy, and (2) architectural changes in the coronary vascular bed.

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During the past decade, Griggs and Buckberg, Hoffman and their associates[13–15] demonstrated that several hemodynamic perturbations can produce marked subendocardial ischemia in normal hearts even when total blood flow increases. Whenever there is a marked decrease in the ratio of supply (estimated as the diastolic pressure-time index × the oxygen-carrying capacity of the blood) to demand (estimated by the tension-time index), subendocardial underperfusion occurs.[13–15] In many conditions associated with cardiac hypertrophy, such as aortic stenosis, aortic regurgitation and patent ductus arteriosus, the supply/demand ratio is markedly altered, particularly during exercise.[14] In these disease states the relative contribution of "hypertrophy per se" and abnormalities in the supply/demand ratio to alterations in transmural myocardial perfusion is difficult to discern.

The effects of alterations in the supply/demand ratio on regional myocardial blood flow have recently been reviewed.[15] In this study we will focus on the effects of hypertrophy on the coronary circulation when the supply/demand ratio is within the normal range.

Effects of Cardiac Hypertrophy on Total Myocardial Blood Flow

Many studies including those performed in our laboratory[16–18] have shown that flow per gram to a hypertrophied ventricle is normal under resting conditions (Fig. 1). Total blood flow to the hypertrophied ventricle is increased in proportion to the magnitude of the hypertrophy. When hypertension is the cause of left ventricular hypertrophy, coronary vascular resistance at rest is elevated markedly (Fig. 2).

When a pressure or volume load is imposed and sufficient time is allowed for the amount of ventricular hypertrophy to reach a plateau, calculated left ventricular wall stress is normal.[19,20] Because the other two major determinants of myocardial oxygen consumption (heart rate and myocardial contractility) are also normal or near normal in the hypertrophied ventricle, flow per gram in a ventricle with stable hypertrophy would be expected to be unaltered.

There is one exception to this general conclusion. Murray et al.[21,22] observed that when the right ventricle is hypertrophied by progressive supravalve pulmonary stenosis, flow per gram to the right ventricle is significantly increased. The explanation for this observation is unclear. Increases in right ventricular wall stress may account for this increase in resting flow. Unfortunately, for technical reasons, right ventricular wall stress cannot be measured directly.

Effects of Cardiac Hypertrophy on Regional Myocardial Blood Flow

Measurements of regional myocardial blood flow in hypertrophied ventricles studied under basal conditions have not shown any abnormalities in the distribution of coronary blood flow from base to apex or circumferentially, that is, septum versus lateral wall.[16] Measurements of the transmural distribution of coronary flow in dogs with short-term (less than 8 weeks) left ventricular hypertrophy secondary to renal hypertension studied in our laboratory have not revealed any abnormalities even when the innermost layers of the left ventricle are examined (Fig. 3). In contrast, preliminary data from our laboratory indicate that in dogs with short-term volume-induced left ventricular hypertrophy secondary to complete heart block[17] or long-term (greater than 6 months) renal hypertension,[18] the endocardial/epicardial flow ratio is significantly less than that observed in normal dogs.

Other investigators have reported that the transmural distribution of myocardial blood flow under basal or control conditions varies from normal to markedly abnormal in various hypertrophy preparations. In pigs[23] and dogs with left ventricular hypertrophy induced by supravalvular aortic stenosis of 6 weeks duration,[24] the transmural distribution of coronary flow is normal. In dogs with long-term (greater than 9 months) supraval-

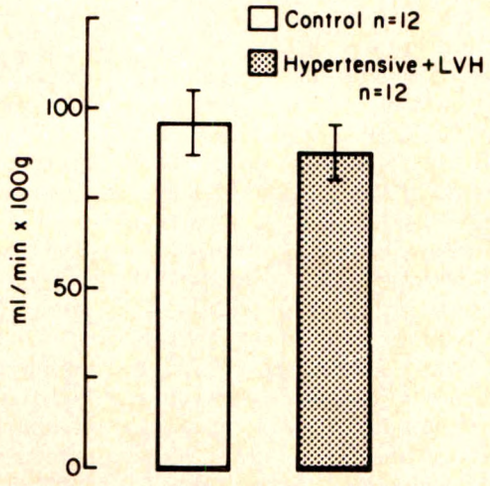

FIGURE 1. Values for left ventricular perfusion in normal and hypertensive dogs with left ventricular hypertrophy (LVH). The perfusions are normalized per 100 g. There is no difference between the control and the hypertensive dogs with left ventricular hypertrophy. n = number of dogs.

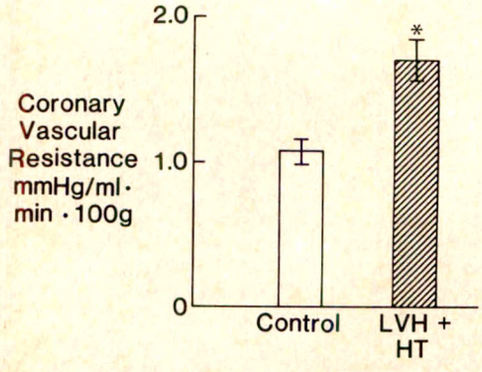

FIGURE 2. Coronary vascular resistance normalized per 100 g in control dogs and dogs with hypertension and left ventricular hypertrophy (LVH + HT). The coronary vascular resistance in the hypertensive dogs with left ventricular hypertrophy is substantially increased. * $P < 0.05$.

vular aortic stenosis and severe left ventricular hypertrophy (100 percent increase in left ventricular mass), endocardial/epicardial flow ratios have been less than normal.[25–28] One group of investigators[26] found in anesthetized dogs that the endocardial/epicardial flow ratio was inversely related to the severity of the left ventricular hypertrophy. In the hypertrophied right ventricle, the transmural distribution of coronary blood flow is normal.[21,22,29]

Mechanisms: The mechanisms responsible for abnormalities in the transmural distribution of coronary flow under basal conditions in some animal models of left ventricular hypertrophy remain to be elucidated. Subendocardial fibrosis is minimal and apparently does not account for this abnormality.[27] Although the decrease in endocardial perfusion in some hypertrophied hearts may reflect an abnormality in the coronary circulation, this is in doubt because all studies have shown that the decrease in the endocardial/epicardial flow ratio occurs even though both the epicardial and endocardial layers have substantial vasodilator reserve. This implies that the decrease in perfusion to the endocardium reflects a decrease in metabolic demand. In the normal ventricle the metabolic demands of the endocardium are greater than those of the epicardium.[15] Although a similar relation may exist in the hypertrophied ventricle, it is possible that in the presence of severe long-standing left ventricular hypertrophy, important alterations may occur in the transmural distribution of wall stress which decreases the metabolic requirements of the endocardium.

Effects of Cardiac Hypertrophy on Vasodilator Reserve in the Coronary Circulation

Although there has been some variability in the effects of cardiac hypertrophy on the transmural distribution of coronary blood flow at rest, almost all studies have shown that cardiac hypertrophy limits vasodilator reserve in the coronary circulation.[16–18,23,24,26–31]

Pharmacologic approaches: Studies in our laboratory have mainly used pharmacologic methods to produce coronary vasodilatation.[16–18] When the coronary bed is dilated maximally by an intravenous infusion of adenosine, the minimal coronary vascular resistance is similar in normal and hypertrophied hearts if the calculation is based on flow to the entire heart (Fig. 4). This implies that the total cross-sectional area of the resistance vessels in the coronary bed of the hypertrophied ventricles has not increased even though the ventricular mass has increased by almost 50 percent. As expected, minimal coronary vascular resistance per gram is significantly increased[16] (Fig. 3).

Because the dogs in our study had hypertension, it was possible that the increase in minimal coronary vascular resistance was functional, that is, secondary to increased systolic compression of the coronary vessels by the hypertensive ventricle. This is unlikely because additional studies demonstrated similar abnormalities in the coronary circulation in dogs with hypertrophy after the hypertension was reversed (Fig. 4 and 5). These studies suggest that left ventricular hypertrophy secondary to renal hypertension is associated with a structural abnormality in the coronary vascular bed that, in effect, prevents the cross-sectional area of the coronary bed from increasing in proportion to the increase in ventricular mass. This could occur because either the growth of resistance vessels is inadequate or an increase in the wall to lumen ratio of the coronary resistance vessels in response to hypertension[32] offsets any vascular growth that does occur.

Preliminary data from our laboratory[17] indicate that in dogs with volume-induced ventricular hypertrophy secondary to chronic complete heart block, the maximal vasodilator capacity of the coronary bed does not in-

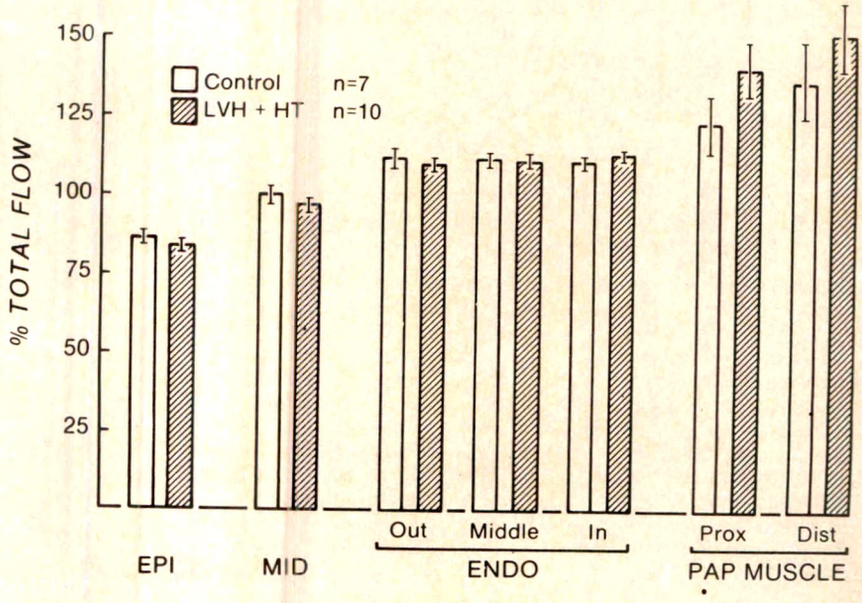

FIGURE 3. Regional distribution of myocardial blood flow in control and hypertensive dogs with left ventricular hypertrophy (LVH + HT). The flows are normalized in cubic centimeters per 100 g and shown as a percent of the total flow of the entire left ventricle. The wall of the left ventricle was divided into three layers of about equal thickness—epicardium (EPI), mid wall (MID) and endocardium (ENDO). Then, the endocardial layer was divided into three additional layers of equal thickness—outer (Out), mid endocardium (Middle) and inner (In). The papillary muscles (PAP MUSCLE) were divided into proximal (Prox) and distal (Dist) segments that were about equal in length. The endocardial layers and the papillary muscles receive more flow per gram than the epicardial layers of the ventricle. However, the dogs with left ventricular hypertrophy and hypertension do not have any abnormalities in the distribution of transmural myocardial perfusion if they are studied 6 weeks after the onset of the hypertension (n = number of dogs).

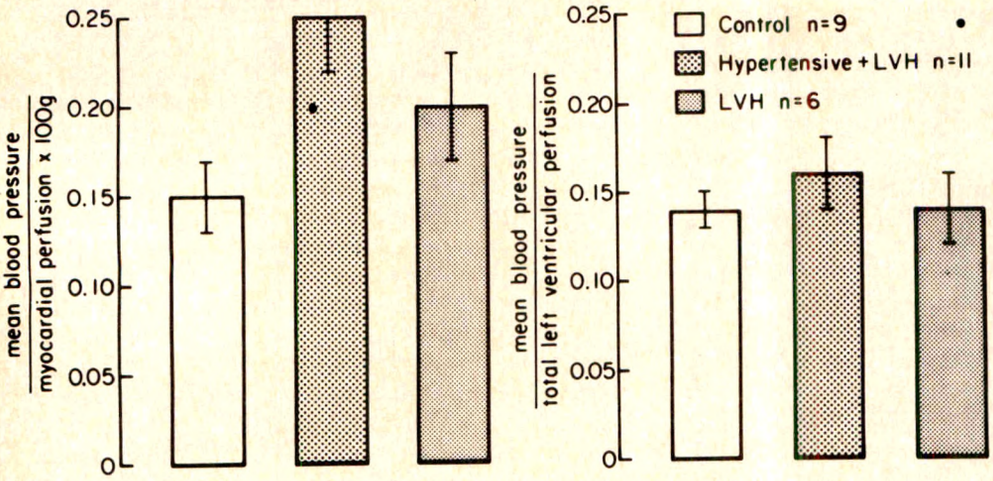

FIGURE 4. Effects of maximal coronary vasodilatation on coronary vascular resistance in normal and hypertrophied ventricles. If coronary vascular resistance is normalized per 100 g **(left panel),** it is significantly increased in dogs with hypertension and left ventricular hypertrophy (LVH) and in dogs with left ventricular hypertrophy alone. If the coronary vascular resistance is calculated for the total left ventricle **(right panel),** the vascular resistance is unchanged in the hypertrophied ventricles. This suggests that the cross-sectional area of the coronary vascular bed is about the same in normal and hypertrophied ventricles. n = number of dogs.

crease in proportion to the extent of hypertrophy. In this model mean arterial pressure is normal, and alterations in the wall to lumen ratio of resistance vessels in the coronary bed would not be expected. Therefore, inadequate vascular growth is probably the cause of the observed abnormalities. Quantitative anatomic studies to assess both vascular growth and the wall to lumen ratio of resistance vessels in the coronary bed will be needed for a further evaluation.

Archie et al.[29] showed that coronary vasodilatation in response to isoproterenol infusion is normal in hypertrophied right ventricles of 5 to 12 week old lambs that had pulmonary arterial banding 24 to 48 hours after birth. O'Keefe et al.[24] showed that maximal coronary vasodilatation is limited in anesthetized dogs with mild left ventricular hypertrophy secondary to supravalve aortic obstruction of 6 weeks' duration. In these studies, maximal coronary vasodilatation was induced with adenosine or carbochrome.

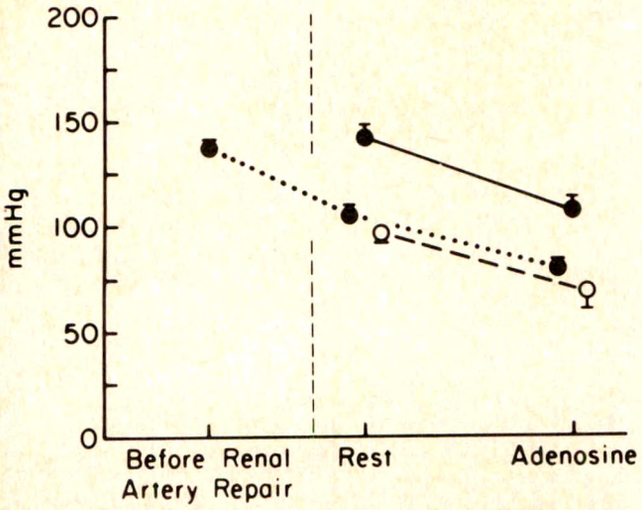

FIGURE 5. Arterial pressure at rest and during adenosine infusion (4.7 μmoles/kg per min intravenously in control dogs (O - - - - O) and dogs with hypertension and left ventricular hypertrophy (● —— ●) and normotension and left ventricular hypertrophy (● ····· ●). Before renal arterial repair, the two groups of dogs with hypertension had similar blood pressures. After repair, the blood pressure in the surgically treated group returned to normal. More important, during adenosine infusion, the dogs with left ventricular hypertrophy that were normotensive had perfusion pressures similar to those of the normal control dogs and substantially less than those of the dogs with hypertension. Thus, the effects of compressive forces on coronary vascular resistance were similar in control dogs and in normotensive dogs with left ventricular hypertrophy.

Physiologic interventions: Studies in our laboratory[16] showed that pacing to heart rates of 200 beats/min is associated with a disproportionate decrease in endocardial/epicardial flow ratio in awake dogs with cardiac hypertrophy secondary to renal hypertension. Vrobel et al.[31] showed that pacing to rates of 250 beats/min in dogs with supravalve aortic stenosis and severe left ventricular hypertrophy is also associated with a modest decrease in the endocardial/epicardial flow ratio in comparison with the normal response.

The response of the coronary circulation of dogs with cardiac hypertrophy to transient coronary occlusion also is abnormal. Rembert et al.[27] noted that in dogs with marked left ventricular hypertrophy the increase in flow to the subendocardium after a 20 second coronary occlusion was less than that observed in normal dogs. Murray and Vatner,[30] who studied dogs with marked right ventricular hypertrophy secondary to progressive supravalve pulmonary stenosis of 1 to 9 months' duration, found that the reactive hyperemia after transient coronary occlusion of the right coronary artery was greatly attenuated.

Six laboratories recently studied the effects of exercise on total or regional coronary blood flow, or both, in pigs or dogs with ventricular hypertrophy.[23,25,26,30,33,34] The results of these studies were variable. At one extreme, Murray and Vatner[30] noted marked abnormalities in response to exercise in dogs with severe right ventricular hypertrophy and failure. In contrast, Vrobel et al.[26] noted that dogs with marked left ventricular hypertrophy had nearly normal myocardial perfusion even when the exercise stress was near maximal levels. Investigators at two laboratories have observed subendocardial underperfusion in hypertro-

phied ventricles during exercise.[23,25] The variable results of these studies are partly related to the severity of the exercise stress employed, the degree and duration of the ventricular hypertrophy, the ventricle involved and the age of the animal when the hemodynamic stress was introduced. Interpretation of these studies is further complicated because treadmill exercise in dogs does not always cause maximal coronary vasodilatation.[35]

In summary, the foregoing studies suggest that several types of cardiac hypertrophy are associated with a decrease in the vasodilator reserve of the coronary circulation. These limitations in coronary reserve become apparent when coronary vasodilatation is elicited by a variety of stimuli including pharmacologic vasodilatation, pacing, transient coronary occlusion and exercise.

Factors That Modulate the Effects of Cardiac Hypertrophy on the Coronary Circulation

The major factors that modulate the effects of cardiac hypertrophy on the coronary circulation can be ascertained only by reviewing data obtained in many laboratories. Although this procedure is less than ideal, it serves to summarize major concepts in this area. At least three factors are probably important in modulating this response: (1) the ventricle that is involved, (2) the duration of the hypertrophy, and (3) the severity of the hypertrophy.

Right versus left ventricular hypertrophy: The adverse effects of hypertrophy on the coronary circulation in the right ventricle in adult dogs are more prominent than those in the left ventricle.[21,22,30] This difference probably occurs because the vasodilator reserve of the adult right ventricle is less than that of the adult left ventricle.

Duration of hypertrophy: This factor also may affect the magnitude of the abnormality observed in the coronary circulation. In our laboratory, preliminary results suggest that when hypertrophy is present for 6 to 8 months verus 6 to 8 weeks, the impairment in maximal coronary vasodilatation is more prominent.[16,18] Furthermore, at rest, the endocardial/epicardial flow ratio is decreased if left ventricular hypertrophy is present for 6 months whereas it is normal at 6 weeks. Studies of coronary dilator capacity in animals with right ventricular hypertrophy also suggest that the duration of hypertrophy and the age the stimulus is applied may be important. Abnormalities have only been demonstrated in adult animals with long-term right ventricular hypertrophy.[21,22,29,30]

Severity of hypertrophy: In general, studies that employed dog models with marked ventricular hypertrophy[21,22,25,27,30] showed the most prominent abnormalities in the coronary circulation, although there are exceptions.[15,26] Other factors such as the stimulus for hypertrophy, the age of the animal at the onset of the stimulus and the rate at which the stimulus is applied may also be important in modulating the response of the coronary circulation to left ventricular hypertrophy.

Future Directions

Many additional studies will be needed before the effects of cardiac hypertrophy on the coronary circulation can be fully understood. Studies that would most likely yield important new information in this area relate to the effects of coronary stenosis and myocardial infarction in hypertrophied ventricles and quantitative anatomic studies of the effects of hypertrophy on the coronary circulation.

Also, research in this area should be directed toward extending the observations made in animals to man. Such studies may uncover major abnormalities in the coronary circulation of patients with ventricular hypertrophy because two major factors (severity and duration of left ventricular hypertrophy) that augment the adverse effects of hypertrophy on the coronary circulation in animals are often intense in man. The recent development of techniques for estimating both transmural[36,37] and phasic coronary blood flow[38] in man should make such studies feasible.

Acknowledgment

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Effects of Exercise on Blood Flow in the Hypertrophied Heart

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This study was carried out to examine the response of regional myocardial blood flow to exercise in normal dogs and in dogs with left ventricular hypertrophy. Left ventricular hypertrophy, with an approximately 50 percent increase in left ventricular mass, was produced by means of perinephritic hypertension. The animals were studied approximately 5 months after the induction of hypertension. Myocardial blood flow to four transmural layers of the left ventricular wall was measured using left atrial injections of 15 μ radioactive microspheres at rest and during two levels of treadmill exercise to increase heart rates to 200 and 260 beats/min, respectively. Mean left ventricular blood flow during resting control conditions was similar in the two groups of dogs. In addition, blood flow increased similarly during exercise so that heart rate or the product of heart rate and systolic blood pressure predicted myocardial blood flow equally well in normal dogs and in those with left ventricular hypertrophy. During resting conditions, subendocardial blood flow significantly exceeded subepicardial blood flow in normal dogs, but exertion abolished this perfusion gradient, resulting in uniform transmural myocardial blood flow during exercise. In contrast, in dogs with left ventricular hypertrophy, blood flow to the subendocardium of the left ventricle significantly exceeded subepicardial blood flow both at rest and during exercise. Nevertheless, this study failed to demonstrate any exercise-induced perfusion deficit within the hypertrophied left ventricle.

Previous clinical and experimental data have demonstrated that the pressure-overloaded hypertrophied heart may exhibit abnormal contractile function, which may eventually lead to cardiac failure.[1–3] Linzbach[4] suggested that the basis for this abnormality may reside in the inability of the coronary vasculature to increase proportionately with the degree of myocardial hypertrophy. In support of this, patients with left ventricular hypertrophy may have angina pectoris and changes in electrocardiographic repolarization consistent with subendocardial ischemia in the absence of demonstrable coronary artery disease.[2] Despite these findings suggesting inadequate coronary perfusion, myocardial blood flow is generally within normal limits in the hypertrophied heart during resting conditions.[5,6] However, any potential perfusion abnormality would be most likely to occur during periods of increased cardiac activity when the ability of the coronary vascular system to deliver blood is maximally taxed. In support of this hypothesis, several recent studies suggest that myocardial blood flow in the hypertrophied heart may not increase normally during coronary vasodilation produced by pharmacologic vasodilators or during reactive hyperemia.[7–9] However, these stimuli for vasodilation may not behave identically with coronary vasodilation, which occurs in response to increased myocardial oxygen consumption.

Because no previous measurements of blood flow in the hypertrophied heart during exercise are available, this study was designed to assess the ability of myocardial blood flow in the hypertrophied heart to respond

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to the physiologic stress of exercise. Studies were carried out in chronically instrumented awake dogs in which left ventricular hypertrophy had been produced by perinephritic hypertension as well as in normal control dogs.

Methods

Production of hypertension: Studies were carried out in 11 adult mongrel dogs weighing 21 to 29 kg. Six dogs served as controls, whereas in five animals left ventricular hypertrophy was produced by means of perinephritic hypertension. The dogs to be made hypertensive were anesthetized with intravenous sodium pentobarbital (25 mg/kg body weight), a left flank incision was made under sterile conditions and the left kidney was dissected free and loosely wrapped in silk. The wrapped kidney was returned to its normal position, the incision closed and the animal allowed to recover. Four to 6 weeks after the initial operation, the dog was reanesthetized and a right nephrectomy was performed with use of a right flank incision. Postoperatively, blood pressure measurements were taken at weekly intervals using a Doppler ultrasound transducer (Arterio-Sonde model 1020); all dogs included in the study sustained at least a 50 mm Hg increase in systolic blood pressure after operation. The reliability of cuff blood pressure measurements was established by comparison with intraarterial pressure obtained by direct puncture of the femoral artery in each dog. After recovery from operation, the animals were trained to run on a motor-driven treadmill.

Experimental preparation: Four to 7 months after the initial operation (mean 5.7 ± 0.7 months), the dogs were anesthetized with sodium pentobarbital (25 mg/kg), ventilated with a respirator and subjected to left thoracotomy at the fourth intercostal space. A polyvinyl catheter, with a 3.5 mm outside diameter, was inserted into the ascending aorta by way of the left internal thoracic artery. Similar catheters were inserted into the left atrium and left ventricle and secured in place with purse-string sutures. The catheters were filled with heparin-saline solution and tunneled into a subcutaneous pouch at the base of the neck. This same surgical procedure was carried out in the six normal control dogs. Retraining on the treadmill was begun 5 to 7 days after operation, and the studies were performed 14 to 21 days after thoracotomy.

Pressure and myocardial blood flow measurements: On the day of study the three catheters were attached to miniature pressure transducers (Ailtech Model MS10) that were fastened at the mid chest level to a nylon vest that the dog had been trained to wear. In addition, the arterial catheter was attached to a constant rate withdrawal pump to facilitate blood sampling. Phasic and mean aortic and mean left atrial pressures, as well as left ventricular pressure at both normal and high gain for measurement of end-diastolic pressure, were recorded continuously on an eight channel direct-writing oscillograph. Measurements of regional myocardial blood flow were made using serial injections of microspheres 15 μ in diameter labeled with gamma-emitting radionuclides cerium-141, strontium-85, and niobium-95 (3M Company), diluted in 10 percent low molecular weight dextran. Before injection the microspheres were mixed for at least 15 minutes in an ultrasonic bath. During each intervention, approximately 3×10^6 microspheres were injected through the left atrial catheter over a 15 second interval. Beginning 5 seconds before injection, a reference sample of arterial blood was withdrawn from the aortic catheter at a constant rate of 15.0 ml/min for 90 seconds. Measurements of myocardial blood flow were made during quiet resting conditions and during two levels of exercise that increased heart rates to approximately 200 beats/min (light exercise) and 260 beats/min (heavy exercise). The mean speed and grade were: light exercise 3.0 miles/hour and 5 percent grade; heavy exercise 4.0 miles/hour and 10 percent grade. Microspheres were injected 3 minutes after the dog had achieved the desired speed and grade, and the exercise was continued for 2 minutes after completion of the injection. Hemodynamic variables were monitored continuously to ensure that a steady state existed before and after the injection of microspheres.

Anatomic myocardial specimens: After completion of the study, the dog was killed with a lethal dose of sodium pentobarbital. The heart was removed and fixed in 10 percent buffered formalin. After fixation, the atria and great vessels, right ventricle and epicardial vessels were dissected from the left ventricle. The left ventricle was then weighed and divided into six circumferential regions representing the intraventricular septum, posterior free wall, posterior papillary muscle region, lateral wall, anterior papillary muscle region and anterior free wall.[10] The myocardium from each region was divided into four transmural layers of equal thickness from epicardium to endocardium, weighed and placed in vials for counting. For the remainder of this report, these layers will be referred to as layers 1 through 4, layer 1 being the most epicardial and layer 4 the most endocardial layer.

Myocardial and blood reference samples were counted in Packard model 5912 gamma counting system at window settings corresponding to the peak energies of each radionuclide. The counts per minute recorded in each energy window were corrected for background activity and for overlapping counts contributed by the accompanying isotopes with a digital computer. Blood flow to each myocardial specimen (Q_m) was computed using the formula $Q_m = Q_r \cdot C_m/C_r$, where Q_r = reference blood flow (ml/min), C_m = counts/min of myocardial

TABLE 1

Hemodynamic Data at Rest and During Two Levels of Exercise in Six Normal Dogs (N) and Five Dogs With Hypertension and Left Ventricular Hypertrophy (LVH)

	Heart Rate (beats/min)		MAP		LVSP		LVEDP	
	N	LVH	N	LVH	N	LVH	N	LVH
Rest	93 ± 6	99 ± 4	92 ± 9	139 ± 15*	124 ± 11	169 ± 16*	4 ± 1	6 ± 2
Exercise								
Light	192 ± 7	200 ± 4	112 ± 8	174 ± 18*	147 ± 11	222 ± 22*	5 ± 2	12 ± 4*
Heavy	250 ± 8	259 ± 8	130 ± 10	198 ± 19*	172 ± 16	258 ± 21*	5 ± 2	13 ± 2*

* P (probability) <0.05 in comparison with normal dogs.
Values are mean ± standard error of the mean.
LVEDP = left ventricular end-diastolic pressure (mm Hg); LVSP = left ventricular systolic pressure (mm Hg); MAP = mean arterial pressure (mm Hg).

specimen and C_r = counts/min of reference blood specimen. The blood flow from each myocardial specimen (ml/min) was divided by sample weight and expressed as milliliters per minute per gram of myocardium. Data from individual myocardial specimens were examined using a threeway analysis of variance test for significant effects of the experimental intervention, the circumferential position and the transmural layer on blood flow. When significant effects were found, pair-wise comparisons were performed to determine where significant differences existed. Because the circumferential position of the myocardial specimen was not found to exert a statistically significant effect on blood flow, data from all six circumferential regions were pooled. Thus, during each intervention all myocardial blood flow data were reduced to the mean values representing the four transmural layers. Mean left ventricular blood flow for each intervention was determined by averaging flow to all left ventricular samples for each dog. Endocardial/epicardial blood flow ratios were obtained by dividing flow to layer 1 by flow to layer 4.

Results

Blood pressures and left ventricular weight (Table I): Mean left ventricular weight for the six normal dogs was 103 ± 5 g whereas the average body weight was 23.6 ± 1.0 kg, with a left ventricular/body weight ratio of 4.3 ± 0.2 g/kg. The body weight of the hypertensive dogs was similar at 24.1 ± 1.2 kg whereas the mean left ventricular weight was increased to 153 ± 16 g ($P < 0.01$), yielding a left ventricular/body weight ratio of 6.4 ± 0.5 g/kg ($P < 0.01$). During resting conditions left ventricular systolic pressure and mean aortic pressure were significantly elevated in the hypertensive dogs whereas left ventricular end-diastolic pressures were similar in the two groups. Exercise resulted in progressive increases of both arterial pressure and left ventricular systolic pressure in both groups, but these increases were significantly greater in dogs with hypertension ($P < 0.05$). Left ventricular end-diastolic pressures were normal in both groups of dogs at rest, but increased significantly during exercise in the hypertensive animals ($P < 0.05$), remaining unchanged in the normal dogs.

Myocardial blood flow (Table II): Mean blood flow per gram of myocardium was similar in the two groups of animals at rest and showed similar progressive increases with exercise. Examination of the relation between mean myocardial blood flow and heart rate showed a close linear correlation between these variables that was virtually identical in the normal dogs and in the dogs with left ventricular hypertrophy (Fig. 1). Similarly, plotting the product of heart rate and systolic blood pressure against myocardial blood flow demonstrated a linear relation that was similar in the normal dogs and in the dogs with left ventricular hypertrophy (Fig. 2). Although myocardial blood flow per unit mass

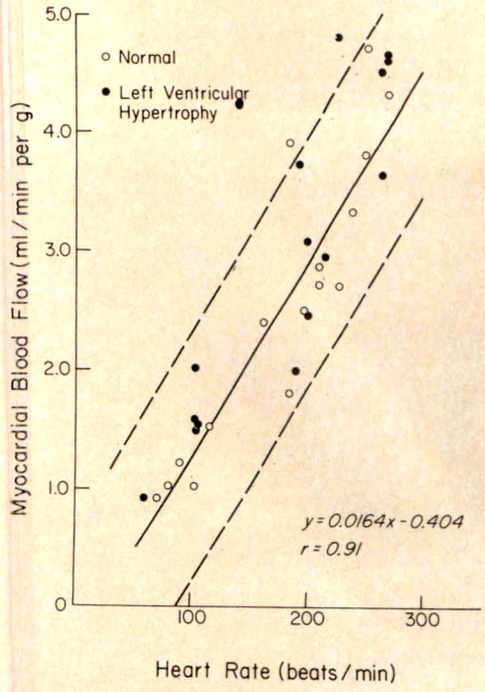

FIGURE 1. Mean left ventricular myocardial blood flow is plotted against heart rate for each dog studied at rest and during light and heavy exercise. The regression equation with 95 percent confidence limits is shown for the six normal animals. There was no significant difference in the relationship of myocardial blood flow to heart rate between the normal dogs and dogs with left ventricular hypertrophy.

TABLE II

Hemodynamic Data at Rest and During Two Levels of Exercise in Six Normal Dogs (N) and Five Dogs With Hypertension and Left Ventricular Hypertrophy (LVH)

Data	Rest		Light Exercise		Heavy Exercise	
	N	LVH	N	LVH	N	LVH
MBF/g (ml/min·g)	1.15 ± 0.11	1.50 ± 0.08	2.69 ± 0.28	2.84 ± 0.29	3.74 ± 0.37	4.43 ± 0.21
MBF/total LV (ml/min)	125 ± 17	239 ± 62*	301 ± 37	473 ± 109*	388 ± 45	708 ± 114*
Endo/Epi	1.28 ± 0.12†	1.32 ± 0.08†	1.13 ± 0.11	1.21 ± 0.06†	1.05 ± 0.08	1.09 ± 0.05
CVR/g of myocardium (mm Hg/ml·min·g)	77.1 ± 6.5	92.7 ± 9.9*	44.6 ± 6.3	62.4 ± 5.5*	36.7 ± 6.0	44.9 ± 3.9
CVR/total LV (mm Hg/ml·min)	0.72 ± 0.06	0.64 ± 0.09	0.42 ± 0.05	0.43 ± 0.05	0.35 ± 0.05	0.30 ± 0.02

* $P < 0.05$ in comparison with normal dogs.
† $P < 0.05$ in comparison with endo/epi of 1.0.
Values are mean ± standard error of the mean. CVR = coronary vascular resistance; Endo/Epi = flow to layer 1/flow to layer 4; LV = left ventricle; LVH = left ventricular hypertrophy; MBF = myocardial blood flow.

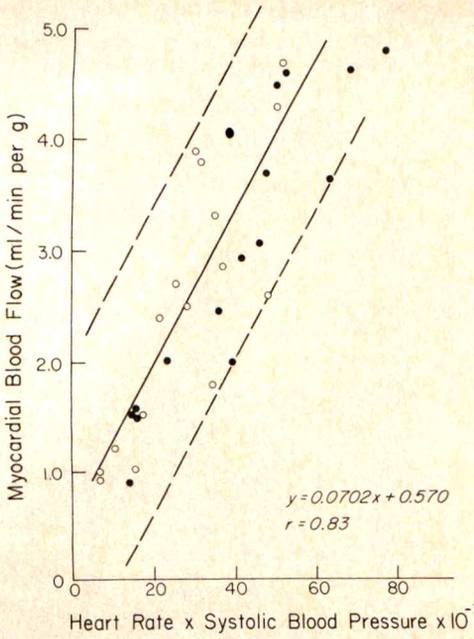

FIGURE 2. Mean left ventricular myocardial blood flow is plotted against the heart rate × systolic blood pressure product for each dog studied at rest and during light and heavy exercise. The regression equation with 95 percent confidence limits is shown for the six normal animals. There was no significant difference in the relationship of myocardial blood flow to the heart rate × systolic blood pressure product between normal dogs and dogs with left ventricular hypertrophy.

was similar in the two groups of dogs, the larger left ventricular mass resulted in a greater total left ventricular blood flow in the hypertensive animals both at rest and during exercise ($P < 0.05$) (Table II). Coronary vascular resistance per unit of myocardial mass was significantly greater in the dogs with left ventricular hypertrophy at rest and during light exercise ($P < 0.05$) but was not significantly different from that in the control dogs during heavy exercise (Table II). However, because of the increased left ventricular mass in the hypertensive dogs, there was no significant difference in total left ventricular coronary vascular resistance between the normal and hypertensive dogs (Table II).

Examination of the transmural distribution of perfusion demonstrated that subendocardial blood flow exceeded subepicardial blood flow in both groups of dogs at rest (Table II). In the normal dogs, exercise resulted in a significant decrease in the endocardial/epicardial flow ratio to values that were not significantly different from unity. In the animals with left ventricular hypertrophy the endocardial/epicardial flow ratio remained significantly greater than 1.0 during light exercise, but decreased to a value not significantly different from unity during heavy exercise.

Discussion

In response to perinephritic hypertension, the dogs in our study sustained an approximately 50 mm Hg increase in resting mean arterial pressure that was associated with an approximately 50 percent increase in relative left ventricular mass. This degree of hypertrophy is similar to that reported from other laboratories[7,11] in which renovascular or perinephritic hypertension was produced in dogs. Renal function, as assessed from serum creatinine and blood urea nitrogen levels, was not compromised throughout the course of this study, and the animals remained vigorous with a normal hematocrit level and stable body weight. In addition, they were able to exercise as well as the normal dogs, so that there was no difference between the two groups of animals in the amount of external work required to attain a given increment in heart rate. Left ventricular end-diastolic pressures were normal at rest in the dogs with left ventricular hypertrophy but increased significantly during exercise. However, because no independent measurement of myocardial mechanical function was available, it is not clear whether this increase in left ventricular end-diastolic pressure during exercise was the result of decreased left ventricular compliance associated with the increased myocardial mass or whether it represented some degree of ventricular dysfunction that became manifest during the stress of exercise.[12]

Myocardial blood flow in normal versus hypertensive dogs: There was no significant difference in blood flow per gram of myocardium at rest or during exercise between the normal dogs and those with left ventricular hypertrophy. This similarity in blood flow between normal and hypertrophied hearts is in agreement with the concept that as the hypertrophic response results in thickening of the left ventricular wall, systolic stress (and thus the myocardial oxygen requirement) decreases in proportion to the increased wall thickness to return to normal or near normal levels.[13] The regression equation relating mean myocardial blood flow (MBF) to heart rate (HR) in both the normal and hypertensive dogs in this study (MBF = 0.0164 HR − 0.404) compares very well with the relation observed in normal human subjects during upright exercise (MBF = 0.0187 HR − 0.650).[14] Thus, the absolute values for myocardial blood flow and the response of myocardial blood flow to exercise appear to be remarkably similar in the normal human heart and in the normal and the hypertrophied dog heart.

Transmural distribution of blood flow in hypertrophied versus normal heart: Few previous data are available on the transmural distribution of myocardial blood flow in the hypertensive heart with left ventricular hypertrophy. Mueller et al.[7] found no difference in the pattern of transmural perfusion between normal and hypertrophied hearts during resting conditions, and flow to the subendocardium exceeded subepicardial flow in both groups. Similarly, in our study subendocardial blood flow exceeded subepicardial flow in both normal and hypertrophied hearts at rest. Because coronary autoregulation appears to regulate blood flow in response to myocardial metabolic needs, the higher subendocardial flow observed in normal hearts may reflect higher oxygen consumption in the subendocardium, a concept that is in agreement with theoretic and experimental data indicating that the

greatest systolic wall stress exists in the subendocardium of the normal heart.[15] In the normal dogs, exercise abolished the transmural heterogeneity of perfusion so that blood flow became essentially uniform. In the hypertrophied heart the transmural perfusion gradient favoring the subendocardium also persisted during light exercise, although it was abolished during heavy exercise. Thus, in this experimental model of left ventricular hypertrophy, exercise did not reveal any tendency toward underperfusion of the subendocardium.

Coronary vasodilation reserve capacity: In dogs with left ventricular hypertrophy secondary to renovascular hypertension, Mueller et al.[7] observed that the maximal cross-sectional area of the total left ventricular coronary bed during coronary vasodilation produced by infusion of adenosine did not appear to increase as hypertrophy of the myocardium occurred. However, because aortic pressure was increased approximately in proportion to the increase in left ventricular mass, the ability to perfuse maximally the left ventricle was not impaired because of the increased coronary perfusion pressure. The animals in our study showed a normal ability to increase myocardial blood flow during exercise, and there was no evidence of impaired coronary perfusion. However, the minimal coronary vascular resistance attained during heavy exercise in this study was still approximately twice the minimal coronary resistance observed by Mueller et al.[7] during adenosine infusion. Thus, even during the relatively heavy level of exercise used in our study, considerable vasodilator reserve capacity would be present within the left ventricular vasculature.

Clinical implications: The data from this study indicate that the heart rate and the product of heart rate and systolic blood pressure may be used to predict myocardial blood flow during exercise in the dog with left ventricular hypertrophy just as they are used in the normal dog heart. The finding that the regression equation describing the relation between myocardial blood flow and heart rate in these dogs was essentially similar to that previously observed in normal human subjects suggests that this relation would also be similar in human subjects with hypertension and left ventricular hypertrophy.[14] Although our study failed to demonstrate any perfusion abnormality at rest or during treadmill exercise in these dogs with left ventricular hypertrophy and a normal coronary arterial anatomy, the occurrence of occlusive coronary artery disease in clinical hypertension and left ventricular hypertrophy would be expected to result in perfusion abnormalities based on the extent of the coronary vascular disease present.

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OCTOBER 1979 THROUGH MARCH 1980

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OCT. 11–13 — **New Concepts in Management of Congestive Heart Failure.** Peter C. Gazes, FACC, director and Charles P. Summerall, III, FACC, Grady H. Hendrix, FACC, William H. Barnwell, II, FACC, Bruce W. Usher, FACC, J. Lindsay Leviner, FACC, Robert G. Irvin and Larry E. Kibler, co-directors. Kiawah Island Inn, Kiawah Island, Charleston, SC

OCT. 18–20 — **Cardiology Update—1979.** William W. Parmley, FACC and Kanu Chatterjee, FACC, directors. Del Monte Hyatt House, Monterey, CA

OCT. 22–23 — **Correlations in Ischemic Heart Disease.** Leonard S. Gettes, FACC, director. Carolina Inn, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC

OCT. 25–27 — **New Techniques and Concepts in Cardiology. Coronary Artery Disease: Rehabilitation, Surgery, Coronary Spasm, Balloon Dilatation; Valvular Heart Disease; Hypertrophic Cardiomyopathy.** Stephen E. Epstein, FACC, director. Hyatt Regency Hotel, Washington, DC

NOV. 5–14 — **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC and James E. Crockett, FACC, directors. Rancho Santa Fe Inn, Rancho Santa Fe, CA

DEC. 2–5 — **Coronary, Valvular, Hypertensive and Myocardial Heart Diseases: The Multi-disciplinary Approach.** William C. Roberts, FACC, director. Williamsburg Conference Center, Williamsburg Lodge, Williamsburg, VA

DEC. 7–9 — **Advances in Heart Disease 1980.** Dean T. Mason, FACC, director. Fairmont Hotel, San Francisco, CA

DEC. 12–14 — **Cross-Sectional Echocardiography vs. Cardiac Nuclear Imaging.** Joel Morganroth, FACC, director. Fairmont Hotel, Philadelphia, PA

DEC. 14–16 — **Twelfth Annual Cardiovascular Symposium: Clinical Decisions in Cardiovascular Disease.** Henry I. Russek, FACC, director. Sheraton Centre, New York, NY

1980

JAN. 14–18 — **Eleventh Annual Cardiovascular Conference at Snowmass.** John H. K. Vogel, FACC, director and Bruce C. Paton, FACC, co-director. Snowmass Resort, Snowmass, CO

JAN. 15 — **Coronary Artery Disease: Diagnosis and Treatment.** William C. Sheldon, FACC and J. Kent Trinkle, directors. Convention Center, San Antonio, TX

JAN.31–FEB. 2 — **Fundamentals of Echocardiography—An Introductory Course for Clinicians.** Joseph K. Perloff, FACC, director and Pravin M. Shah, FACC and John S. Child, FACC, co-directors. Century Plaza Hotel, Los Angeles, CA

FEB. 13–15 — **Cardiac Diagnosis: Reappraisal of Established Techniques and the Place for New Techniques.** Ralph Shabetai, FACC, John Ross, Jr., FACC, Gabriel Gregoratos, FACC and Joel S. Karliner, FACC, directors. Vacation Village Hotel, San Diego, CA

MAR. 24–28 — **Thirteenth Annual Seminar on Electrocardiographic Interpretation of Complex Arrhythmias: A Physiological Approach.** Charles Fisch, FACC and Douglas P. Zipes, FACC, directors. Indianapolis University Medical Center, Indianapolis, IN

LEARNING CENTER: PROGRAM CALENDAR

The American College of Cardiology's newest department, the Learning Center, located at the College's Bethesda Maryland headquarters, began operations in October 1977 with the offering of its first continuing medical education program for physicians with a specialty or an interest in cardiovascular medicine. The purpose of the Learning Center is to support the professional commitment to quality patient care by providing a new standard of excellence in cardiovascular continuing education. For additional information concerning the programs listed below or for a complete schedule of programs through December 1979, contact Program Coordinator, Learning Center, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20014. Telephone (301) 897-5400.

OCTOBER 1979 THROUGH MAY 1980

Month/Dates	Program Director	Title of Program
Oct. 8–11	Leonard S. Dreifus, MD	**Mechanisms and Therapy of Cardiac Arrhythmias**
Oct. 15–17	Marvin Moser, MD	**Hypertension**
Oct. 29–31	Max Harry Weil, MD	**Emergency Care of the Critically Ill Patient**
Nov. 1–3	Barrie Levitt, MD	**Cardiovascular Therapeutics**
Nov. 28–30	William W. Parmley, MD	**Non-Invasive Cardiovascular Procedure: Principles and Clinical Application**
Jan. 21–24	William C. Roberts, MD	**Congenital Heart Disease**
Jan. 28–30	Gottlieb Friesinger, MD	**Coronary Artery Surgery**
Feb. 6–8	Bertram Pitt, MD	**Nuclear Cardiology**
Feb. 13–15	Melvin L. Marcus, MD	**New Approaches to the Short and Long Term Treatment of Myocardial Infarction**
Feb. 18–20	Roger A. Winkle, MD	**Antiarrhythmic Therapy: Current Status and Future Promise**
March 24–26	John A. Mantle, MD	**Quality Assurance and Management for Cardiovascular Nurses**
March 27–29	John Spittell, MD	**Peripheral Vascular Disease**
April 9–11	Victor Parsonnet, MD	**Current Concepts in Pacing**
April 14–16	Keith Cohn, MD	**Exercise Testing**
April 21–23	Nanette Wenger, MD	**Cardiac Rehabilitation**
April 28–30	Pravin M. Shah, MD	**M-Mode and 2-Dimensional Echocardiography: Current Status and Future Promise**
May 1–3	Daniel S. Berman, MD	**Nuclear Cardiology**
May 5–7	Robert G. Tancredi, MD	**Pulmonary, Renal and Electrolyte Considerations in Cardiovascular Disease**
May 12–14	Louis Lemberg, MD	**CCU Update for Nursing Supervisors**
May 19–21	Arthur E. Weyman, MD	**Cross-Sectional Echocardiography**

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DESCRIPTION:
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Potassium is contraindicated in severe renal impairment involving oliguria, anuria or azotemia; in untreated Addison's disease, familial periodic paralysis, acute dehydration, heat cramps, hyperkalemia from any cause. Potassium chloride should not be employed in patients receiving potassium-sparing agents such as aldosterone antagonists and triamterene.

PRECAUTIONS:
KATO is a concentrate and should be taken only after reconstituting with water as directed. This preparation, like other potassium supplements, must be properly diluted to avoid the possibility of gastrointestinal irritation. Do not use in patients with low urinary output or renal decompensation. Administer with caution; it is impossible to assess accurately the daily dose required. Excessive dosage may result in potassium intoxication. Frequent checks of the clinical status of the patient, ECG and/or plasma potassium level should be made. High plasma concentrations of potassium ion may cause death through cardiac depression, arrhythmias or arrest. Use with caution in patients with cardiac disease.

ADVERSE REACTIONS:
Vomiting, diarrhea, nausea, and abdominal discomfort may occur. Gross overdosage may produce signs and symptoms of potassium intoxication: mental confusion, listlessness, paresthesia of the extremities, weakness and heaviness of legs, flaccid paralysis, hyperkalemia, ECG abnormalities, fall in blood pressure, cardiac arrhythmias and heart block. The characteristic changes in the ECG are disappearance of the P wave, widening and slurring of QRS complex, changes of the S-T segment, tall peaked T waves, etc.

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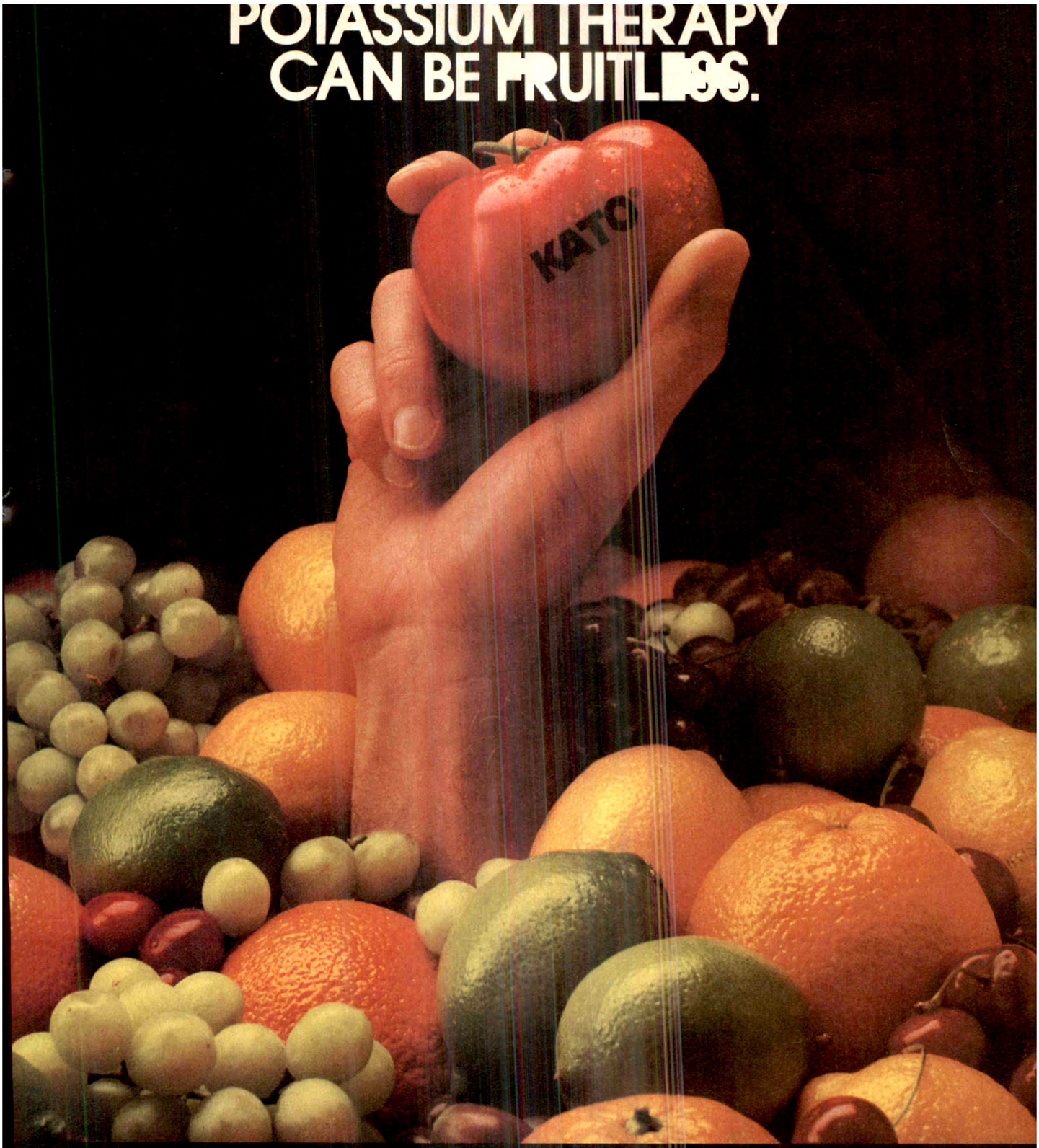

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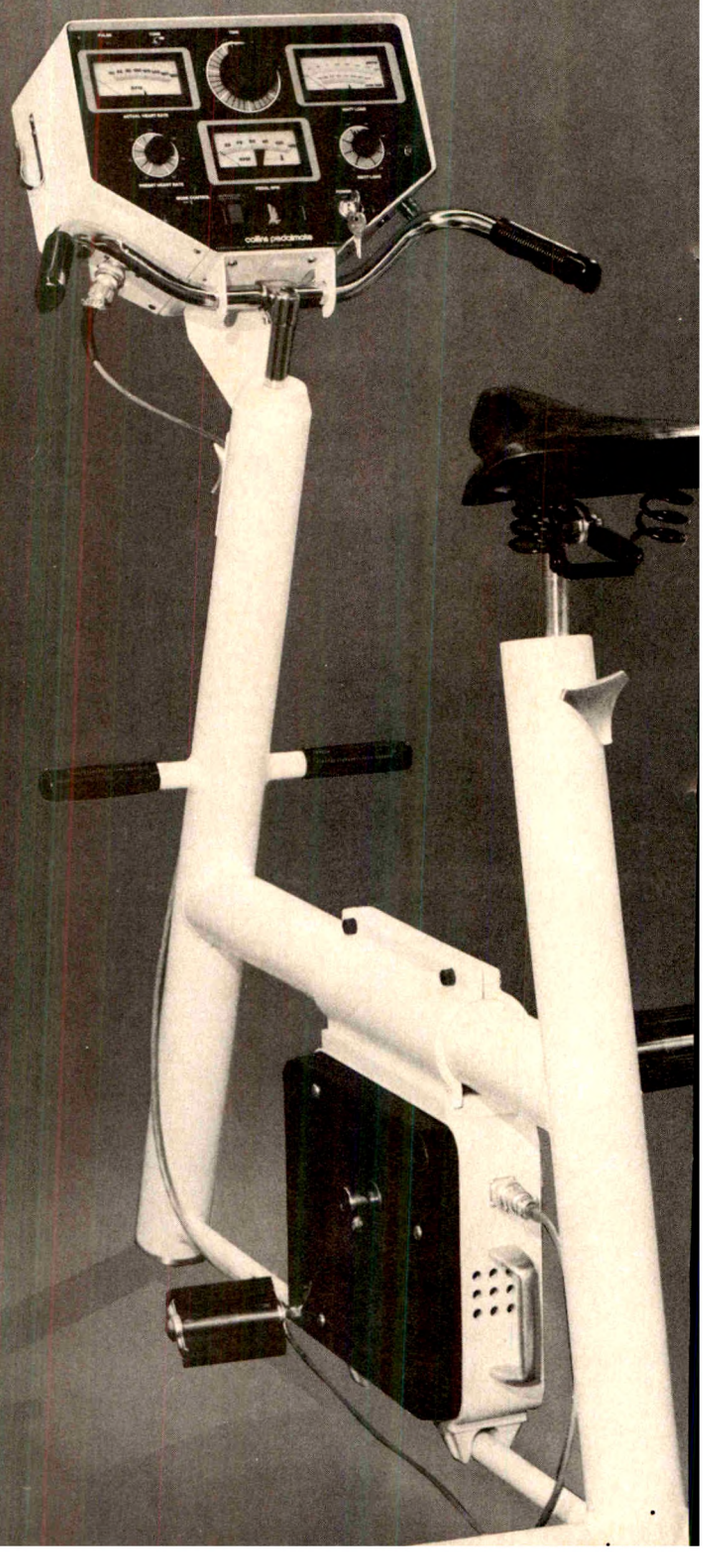

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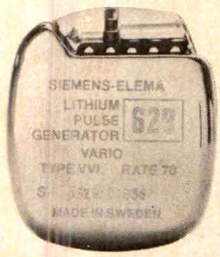

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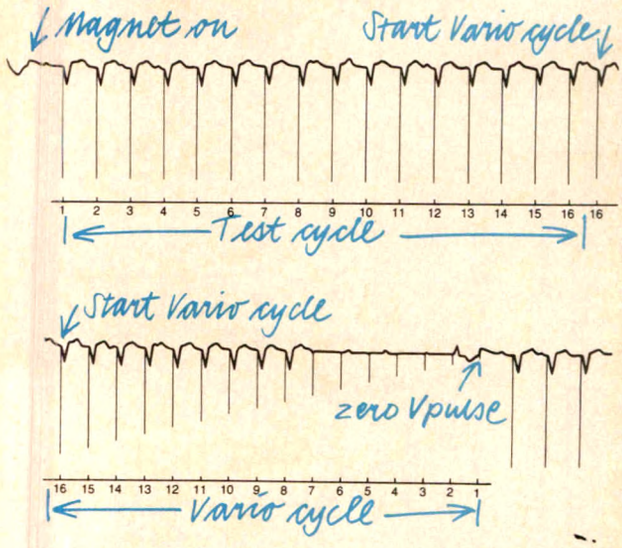

Magnet placed over implanted generator starts test sequence: Battery test cycle (phase 1). Vario cycle (phase 2) for threshold determination.

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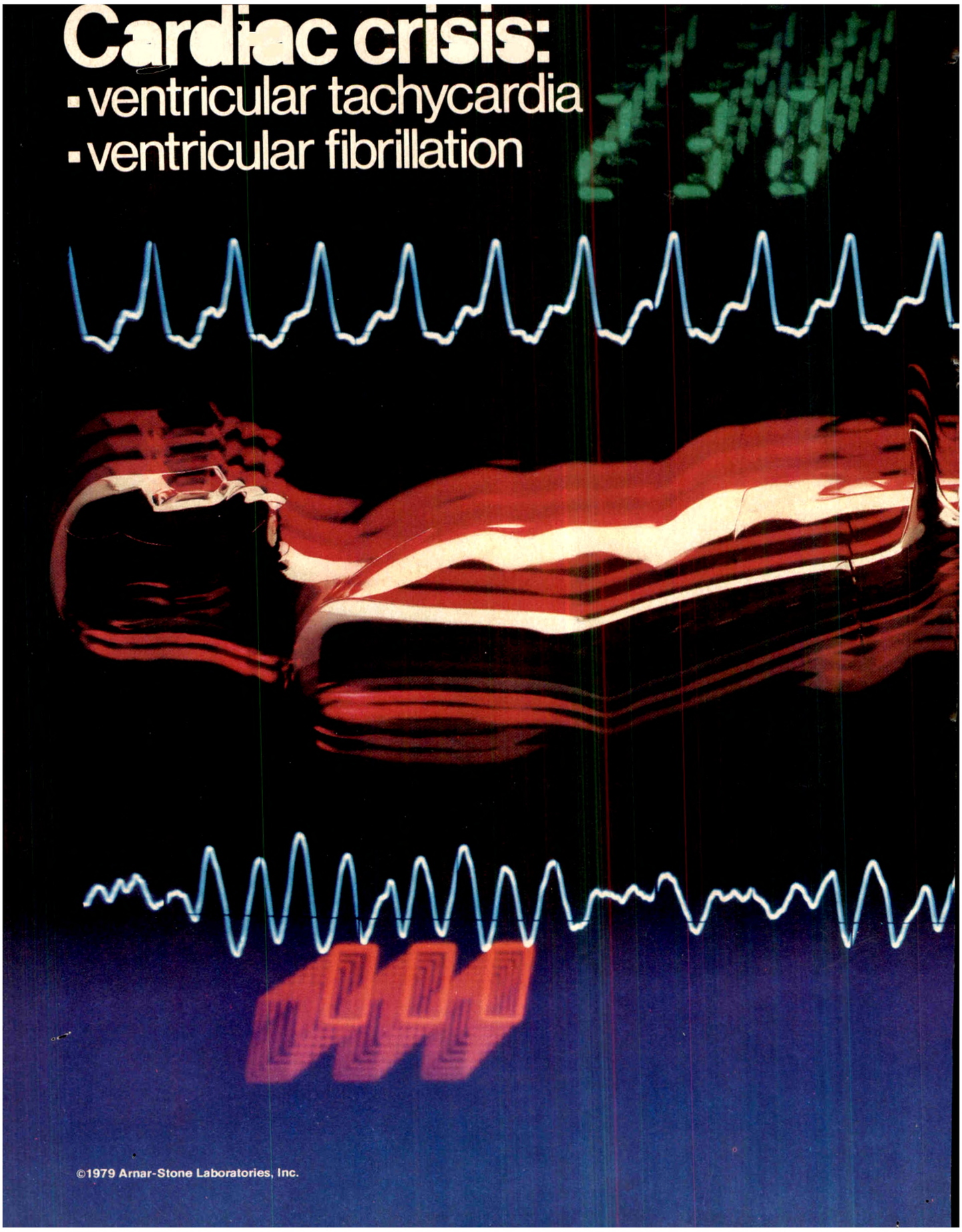
Cardiac crisis:
▪ ventricular tachycardia
▪ ventricular fibrillation
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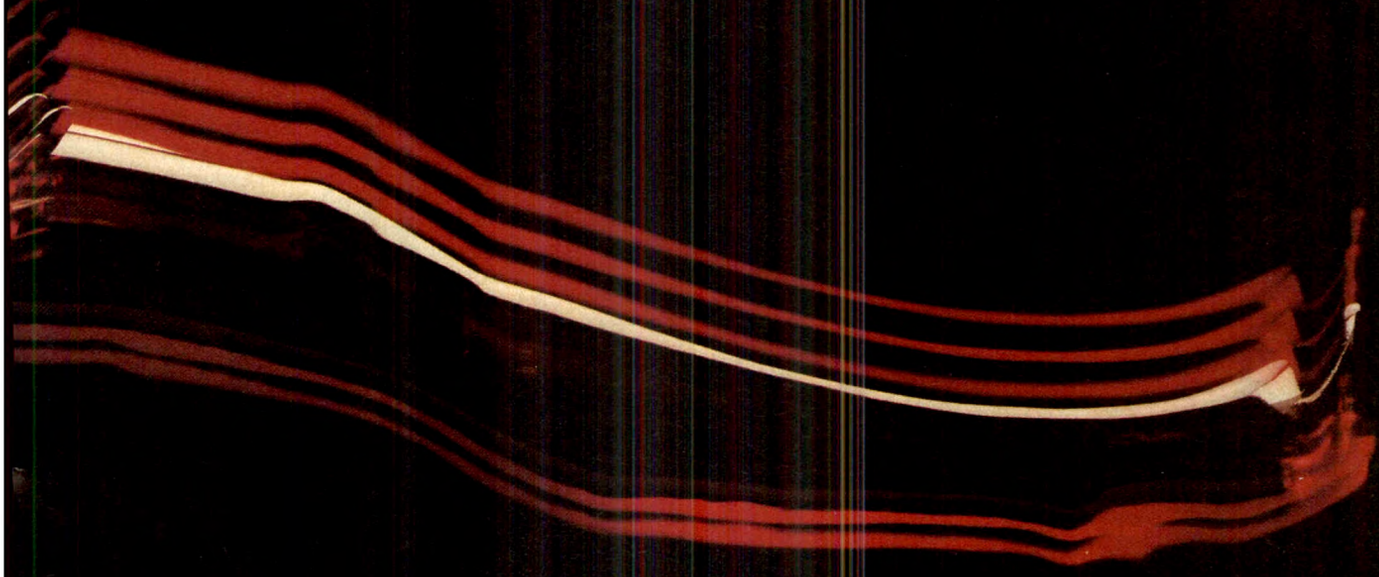
(bretylium tosylate)

Unique antifibrillatory-antiarrhythmic effect
Unique mechanism of action
Unique safety: no cardiac depression



Bretylol® (bretylium tosylate), the unique new antifibrillatory-antiarrhythmic, provides lifesaving effects in the suppression of life-threatening ventricular arrhythmias unresponsive to lidocaine.

See last page of this advertisement for prescribing information.

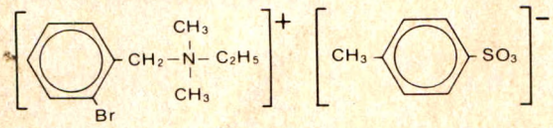
BRETYLOL® bretylium tosylate

BRETYLOL INJECTION

FOR INTRAMUSCULAR OR INTRAVENOUS USE

DESCRIPTION

BRETYLOL (bretylium tosylate) is o-Bromobenzyl ethyldimethylammonium p-toluene sulfonate. The chemical structure is:



$C_{18}H_{24}BrNO_3S$ Mol. Wt. 414.39

BRETYLOL is a white, crystalline powder with an extremely bitter taste. It is freely soluble in water and alcohol. Each ml of sterile, pyrogen-free solution contains 50 mg bretylium tosylate in Water for Injection, USP. The pH is adjusted, when necessary, with dilute hydrochloric acid or sodium hydroxide. BRETYLOL contains no preservative.

CLINICAL PHARMACOLOGY

BRETYLOL (bretylium tosylate) is a bromobenzyl quaternary ammonium compound which selectively accumulates in sympathetic ganglia and their postganglionic adrenergic neurons where it inhibits norepinephrine release by depressing adrenergic nerve terminal excitability.

BRETYLOL also suppresses ventricular fibrillation and ventricular arrhythmias. The mechanisms of the antifibrillatory and antiarrhythmic actions of BRETYLOL are not established. In efforts to define these mechanisms, the following electrophysiologic actions of BRETYLOL have been demonstrated in animal experiments:

1. Increase in ventricular fibrillation threshold.

2. Increase in action potential duration and effective refractory period without changes in heart rate.

3. Little effect on the rate of rise or amplitude of the cardiac action potential (Phase 0) or in resting membrane potential (Phase 4) in normal myocardium. However, when cell injury slows the rate of rise, decreases amplitude, and lowers resting membrane potential, BRETYLOL restores these parameters toward normal.

4. Increase in impulse formation and spontaneous firing rate of pacemaker tissue as well as increased ventricular induction velocity.

The restoration of injured myocardial cell electrophysiology toward normal, as well as the increase of the action potential duration and effective refractory period without changing their ratio to each other, may be important factors in suppressing re-entry of aberrant impulses and decreasing induced dispersion of local excitable states.

BRETYLOL induces a chemical sympathectomy-like state which resembles a surgical sympathectomy. Catecholamine stores are not depleted by BRETYLOL, but catecholamine effects on the myocardium and on peripheral vascular resistance are often seen shortly after administration because BRETYLOL causes an early release of norepinephrine from the adrenergic postganglionic nerve terminals. Subsequently, BRETYLOL blocks the release of norepinephrine in response to neuron stimulation. Peripheral adrenergic blockade regularly causes orthostatic hypotension but has less effect on supine blood pressure. The relationship of adrenergic blockade to the antifibrillatory and antiarrhythmic actions of BRETYLOL is not clear. In a study in patients with frequent ventricular premature beats, peak plasma concentration of BRETYLOL and peak hypotensive effects were seen within one hour of intramuscular administration, presumably reflecting adrenergic neuronal blockade. However, suppression of premature ventricular beats was not maximal until 6-9 hours after dosing, when mean plasma concentration had declined to less than one-half of peak level. This suggests a slower mechanism, other than neuronal blockade, was involved in suppression of the arrhythmia. On the other hand, antifibrillatory effects can be seen within minutes of an intravenous injection, suggesting that the effect on the myocardium may occur quite rapidly.

BRETYLOL has a positive inotropic effect on the myocardium, but it is not yet certain whether this effect is direct or is mediated by catecholamine release.

BRETYLOL is eliminated intact by the kidneys. No metabolites have been identified following administration of BRETYLOL in man and laboratory animals. In man, approximately 70 to 80% of a ^{14}C-labelled intramuscular dose is excreted in the urine during the first 24 hours, with an additional 10% excreted over the next three days.

In various studies of BRETYLOL excretion, estimates of the terminal half-life have varied from about 5 to about 10 hours, with an even wider range in individual subjects (4 to 17 hours). Whether this represents true intrapatient variability or limitations of methodology remains to be determined.

Effect on Heart Rate: There is sometimes an initial small increase in heart rate when BRETYLOL is administered, but this is an inconsistent and transient occurrence.

Hemodynamic Effects: Following intravenous administration of 5 mg/kg of BRETYLOL to patients with acute myocardial infarction, there was a mild increase in arterial pressure, followed by a modest decrease, remaining within normal limits throughout. Pulmonary artery pressures, pulmonary capillary wedge pressure, right atrial pressure, cardiac index, stroke volume index, and stroke work index were not significantly changed. These hemodynamic effects were not correlated with antiarrhythmic activity.

Onset of Action: Suppression of ventricular fibrillation is rapid, usually occurring within minutes following intravenous administration. Suppression of ventricular tachycardia and other ventricular arrhythmias develops more slowly, usually 20 minutes to 2 hours after parenteral administration.

INDICATIONS

BRETYLOL is indicated in the treatment of life-threatening ventricular arrhythmias, principally ventricular fibrillation and ventricular tachycardia, that have failed to respond to adequate doses of a first-line antiarrhythmic agent, such as lidocaine or procainamide. At this time, BRETYLOL should not be considered a first-line antiarrhythmic agent.

Use of BRETYLOL should be limited to intensive care units, coronary care units or other facilities where equipment and personnel for constant monitoring of cardiac arrhythmias and blood pressure are available.

Following injection of BRETYLOL there may be a delay of 20 minutes to 2 hours in the onset of antiarrhythmic action, although it appears to act within minutes in ventricular fibrillation. The delay in effect appears to be longer after intramuscular than after intravenous injection.

CONTRAINDICATIONS

There are no contraindications to use in treatment of ventricular fibrillation or life-threatening refractory ventricular arrhythmias.

WARNINGS

1. Hypotension: Administration of BRETYLOL regularly results in postural hypotension, subjectively recognized by dizziness, light-headedness, vertigo or faintness. Some degree of hypotension is present in about 50% of patients while they are supine. Hypotension may occur at doses

Hypotension with supine systolic pressure greater than 75 mm Hg need not be treated unles
are associated symptoms. If supine systolic pressure falls below 75 mm Hg, an infusion of d
or norepinephrine may be used to raise blood pressure. When catecholamines are adminis
dilute solution should be employed and blood pressure monitored closely because the
effects of the catecholamines are enhanced by BRETYLOL. Volume expansion with blood or
and correction of dehydration should be carried out where appropriate.

2. Transient Hypertension and Increased Frequency of Arrhythmias: Due to th
release of norepinephrine from adrenergic postganglionic nerve terminals by BRETYLOL, t
hypertension or increased frequency of premature ventricular contractions and other arrh
may occur in some patients.

3. Caution During Use with Digitalis Glycosides: The initial release of norepinephrine
by BRETYLOL may aggravate digitalis toxicity. When a life-threatening cardiac arrhythmia
in a digitalized patient, BRETYLOL should be used only if the etiology of the arrhythmia
appear to be digitalis toxicity and other antiarrhythmic drugs are not effective. Simu
initiation of therapy with digitalis glycosides and BRETYLOL should be avoided.

4. Patients with Fixed Cardiac Output: In patients with fixed cardiac output (i.e., sever
stenosis or severe pulmonary hypertension) BRETYLOL should be avoided since severe hyp
may result from a fall in peripheral resistance without a compensatory increase in cardiac
If survival is threatened by the arrhythmia, BRETYLOL may be used but vasoconstrictive
amines should be given promptly if severe hypotension occurs.

USE IN PREGNANCY

The safety of BRETYLOL in human pregnancy has not been established. However, as the
intended for use only in life-threatening situations, it may be used in pregnant women
benefits outweigh the potential risk to the fetus.

USE IN CHILDREN

The safety and efficacy of this drug in children has not been established. BRETYLOL h
administered to a limited number of pediatric patients, but such use has been inadequate t
fully proper dosage and limitations for use.

PRECAUTIONS

1. Dilution for Intravenous Use: BRETYLOL should be diluted (one part BRETYLOL v
parts of Dextrose Injection, USP or Sodium Chloride Injection, USP) prior to intravenous us
intravenous administration may cause severe nausea and vomiting. Therefore, the diluted
should be infused over a period greater than 8 minutes. In treating existing ventricular fi
BRETYLOL should be given as rapidly as possible and may be given without dilution.

2. Use Various Sites for Intramuscular Injection: When injected intramuscularly, r
than 5 ml should be given in a site, and injection sites should be varied since repeat
muscular injection into the same site may cause atrophy and necrosis of muscle tissue,
vascular degeneration and inflammatory changes.

3. Reduce Dosage in Impaired Renal Function: Since BRETYLOL is excreted p
via the kidney, dosage should be reduced in patients with impaired renal function.

ADVERSE REACTIONS

Hypotension and postural hypotension have been the most frequently reported adverse
(see Warnings section). Nausea and vomiting occurred in about three percent of patients,
when BRETYLOL was administered rapidly by the intravenous route (see Precautions
Vertigo, dizziness, light-headedness and syncope, which sometimes accompanied postu
tension, were reported in about 7 patients in 1000.

Bradycardia, increased frequency of premature ventricular contractions, transitory hype
initial increase in arrhythmias (see Warnings section), precipitation of anginal attacks, ar
tion of substernal pressure have also been reported in a small number of patients, i.e., appr
1-2 patients in 1000.

Renal dysfunction, diarrhea, abdominal pain, hiccups, erythematous macular rash,
hyperthermia, confusion, paranoid psychosis, emotional lability, lethargy, generalized te
anxiety, shortness of breath, diaphoresis, nasal stuffiness and mild conjunctivitis, have beer
in about 1 patient in 1000. The relationship of BRETYLOL administration to these react
not been clearly established.

DOSAGE AND ADMINISTRATION

BRETYLOL is to be used clinically only for treatment of life-threatening ventricular ar
under constant electrocardiographic monitoring. Since there is a delay in onset of its antia
action, BRETYLOL is not to be considered or used as a replacement for rapidly-acting antia
agents currently in use. The clinical use of BRETYLOL is for short-term use only. Patien
either be kept supine during the course of BRETYLOL therapy or be closely observed fo
hypotension. The optimal dose schedule for parenteral administration of BRETYLOL has
determined. There is comparatively little experience with dosages greater than 30 m
although such doses have been used without apparent adverse effects. The following sc
suggested:

A. For Immediately Life-threatening Ventricular Arrhythmia, as in Ventricular Fib
Administer undiluted BRETYLOL at a dosage of 5 mg/kg of body weight by rapid in
injection. Other usual cardiopulmonary resuscitative procedures, including electrical card
should be employed prior to and following the injection in accordance with good medical
If ventricular fibrillation persists, the dosage may be increased to 10 mg/kg and repeated
30 minute intervals until a total dose of not more than 30 mg/kg of body weight has been
maintenance dosage, see below.

B. Other Ventricular Arrhythmias:

1. Intravenous Use: *BRETYLOL must be diluted as follows before intravenous administrat*
aseptic technique, dilute contents of one BRETYLOL ampul (10 ml containing 500 mg
tosylate) to a minimum of 50 ml with Dextrose Injection, USP or Sodium Chloride Injection, U

Administer the diluted solution at a dosage of 5 to 10 mg BRETYLOL per kg of body
intravenous infusion over a period greater than 8 minutes. More rapid infusion may caus
and vomiting. A second dose may be given in 1 to 2 hours if the arrhythmia persists.

2. For Intramuscular Injection: *(Do not dilute BRETYLOL prior to intramuscular*
Inject 5 to 10 mg BRETYLOL per kg of body weight. Dosage may be repeated in 1 to 2 h
arrhythmia persists. Thereafter maintain with same dosage every 6 to 8 hours.

Intramuscular injection should not be made directly into or near a major nerve, and t
injection should be varied on repeated injection.

C. Maintenance Dosage: The diluted BRETYLOL solution may be administered by in
bolus infusion or by constant infusion.

1. Intermittent Infusion: Infuse the diluted solution at a dosage of 5 to 10 mg BRETYL
body weight, over a period greater than 8 minutes, every 6 hours. More rapid infusion r
nausea and vomiting.

2. Constant Infusion: Infuse the diluted solution at a dosage of 1 to 2 mg BRETYLOL p

Dosage of BRETYLOL should be reduced and discontinued in 3 to 5 days under electrocar
monitoring. Other appropriate antiarrhythmic agents should be substituted, if indicated.

HOW SUPPLIED

NDC 0094-0012-10: 10 ml ampul containing 500 mg bretylium tosylate in Water for Injec
pH adjusted, when necessary, with dilute hydrochloric acid or sodium hydroxide. Sterile
free.

ARNAR-STONE LABORATORIES, INC.

cordis®

Omni-Stanicor® θ
Lithium-Powered,
Programmable,
R-Wave Inhibited
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For ventricular arrhythmias.
For atrial arrhythmias.
For smooth, trouble-free conversion.
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TABLETS
(quinidine polygalacturonate)

- ☐ Greater GI tolerance than with quinidine sulfate
- ☐ Full quinidine cardiodynamics
- ☐ Convenient b.i.d. or t.i.d. dosage for most patients

CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of a broad range of cardiac arrhythmias (see Brief Summary). After conversion to normal sinus rhythm—whether with CARDIOQUIN Tablets or electroconversion—only low b.i.d. or t.i.d. dosage of this unique polygalacturonate salt of quinidine is required for maintenance in most cases. The polygalacturonic acid serves as a buffering moiety. It protects the mucosa of the stomach and permits dependable absorption of the quinidine.*

*Aviado, D. M., Krantz and Carr's Pharmacologic Principles of Medical Practice, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heart-block; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 100.

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NOVEMBER 1979

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Exercise Testing: Arrhythmias, Hemodynamics, Ischemic Changes

Surgery for Ventricular Arrhythmias

Straddling Atrioventricular Valves

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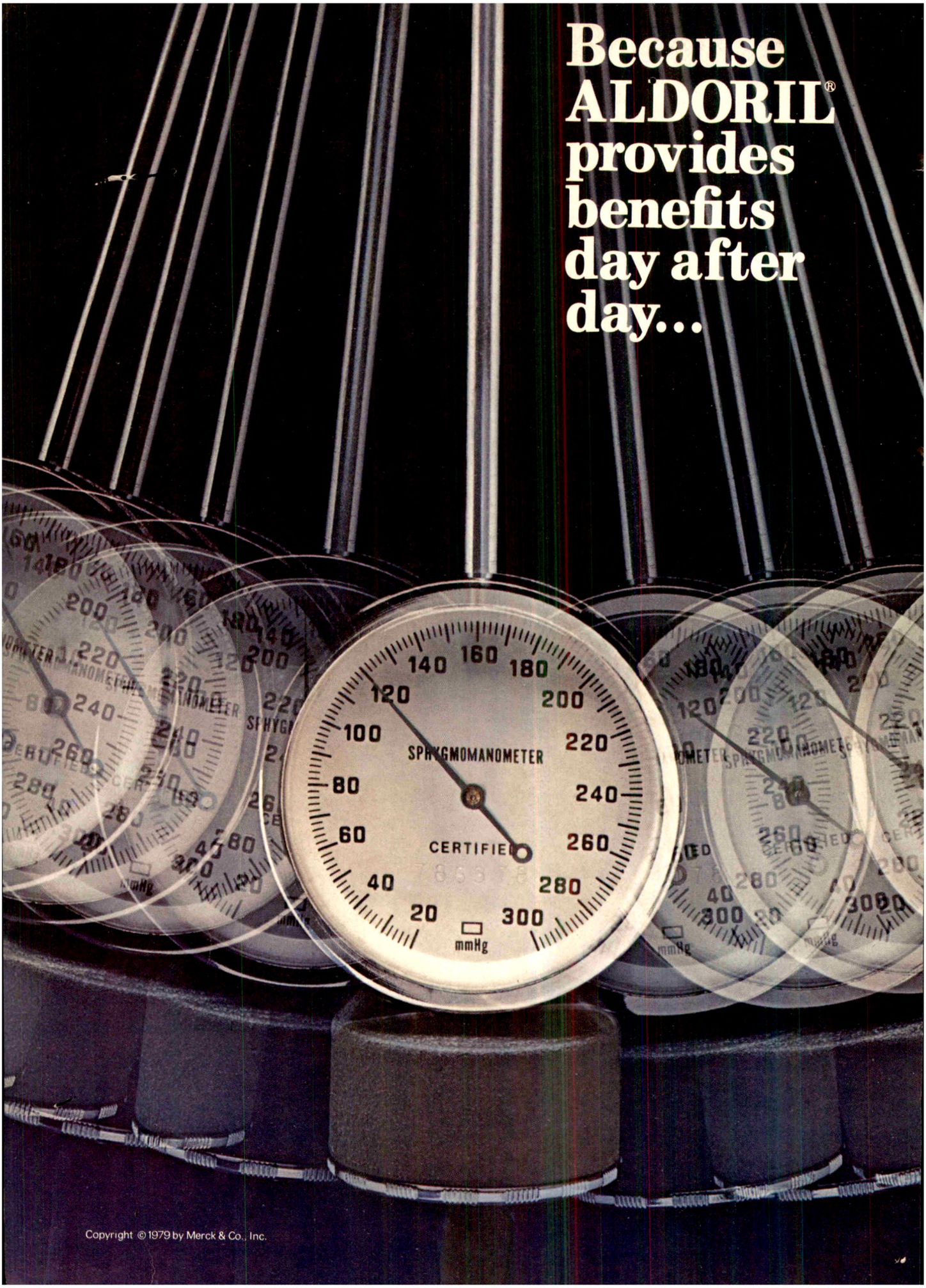
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- **sodium and fluid retention generally controlled**
- **two highly effective complementary agents**

As a fixed combination, ALDORIL is not indicated for initial therapy since hypertension requires therapy titrated to the individual patient. If an available strength of ALDORIL meets the patient's titrated needs, the combination drug may be more convenient in patient management. Therapy should be reevaluated as necessary.

ALDORIL is contraindicated in active hepatic disease; anuria; hypersensitivity to methyldopa or to hydrochlorothiazide or other sulfonamide-derived drugs; if previous methyldopa therapy has been associated with liver disorders. In patients with renal disease, thiazides may precipitate azotemia. Use with caution in patients with severe renal disease or impaired hepatic function.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details, see the brief summary of prescribing information.

For a brief summary of prescribing information, please see following page.

practical benefits

- **effects on daily activities usually minimal:** There is less frequent symptomatic postural hypotension with ALDORIL than with many other antihypertensive agents. Exercise hypotension and diurnal blood pressure variations rarely occur.
- **greater dosage convenience:** a b.i.d. regimen is possible for many patients
- **four dosage strengths:** offer the widest range of dosage strengths available in a combination antihypertensive

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Antihypertensive TABLETS

ALDORIL®-15
methyldopa 250 mg and hydrochlorothiazide 15 mg

WARNING

This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see **Warnings**); anuria; routine use in an otherwise healthy pregnant woman with or without mild edema; hypersensitivity to methyldopa or to hydrochlorothiazide or other sulfonamide-derived drugs.

Warnings: METHYLDOPA—**It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.**

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within the first three weeks of therapy, sometimes with eosinophilia or abnormalities in one or more liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually within the first two to three months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever, abnormalities in liver function tests, or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, reversible reduction of white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Follow patients carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

HYDROCHLOROTHIAZIDE—Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects may develop in patients with impaired renal function. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. May add to or potentiate action of other antihypertensive drugs; potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity; read circulars for lithium preparations before use of such concomitant therapy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant requires that anticipated benefits be weighed against possible risks.

Methyldopa and thiazides cross the placental barrier and appear in cord blood.

No unusual adverse reactions have been reported in association with the use of methyldopa during pregnancy. Although no obvious teratogenic effects have been reported, the possibility of fetal injury cannot be excluded.

The hazards of thiazides crossing the placental barrier include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in adults. Methyldopa and thiazides appear in breast milk. Patients taking ALDORIL should not nurse.

Precautions: METHYLDOPA—Should be used with caution in patients with history of previous liver disease or dysfunction (see **Warnings**). May interfere with measurement of urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites. Involuntary choreoathetotic movements have been observed in patients with severe bilateral cerebrovascular disease. If such movements occur, stop the drug. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

HYDROCHLOROTHIAZIDE—Perform periodic determination of serum electrolytes to detect possible electrolyte imbalance. Observe all patients for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, in severe cirrhosis, with concomitant corticosteroids or ACTH, or with inadequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest. Thiazides may increase responsiveness to tubocurarine. Antihypertensive effects of the drug may be enhanced in postsympathectomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid glands with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged therapy; thiazides should be discontinued before testing for parathyroid function.

Adverse Reactions: METHYLDOPA—*Central nervous system:* Sedation, headache, asthenia or weakness; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression. *Cardiovascular:* Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.) *Gastrointestinal:* Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis. *Hepatic:* Abnormal liver function tests, jaundice, liver disorders. *Hematologic:* Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells and rheumatoid factor. *Allergic:* Drug-related fever, lupus-like syndrome, myocarditis. *Other:* Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

HYDROCHLOROTHIAZIDE—*Gastrointestinal system:* Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis. *Central nervous system:* Dizziness, vertigo, paresthesias, headache, xanthopsia. *Hematologic:* Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, hemolytic anemia. *Cardiovascular:* Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics). *Hypersensitivity:* Purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), fever, respiratory distress including pneumonitis, anaphylactic reactions. *Other:* Hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, transient blurred vision. Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

Note: Tolerance may occur, usually between the second and third month of therapy. Increasing dosage of either component separately or together frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets ALDORIL®-15, containing 250 mg methyldopa and 15 mg hydrochlorothiazide, bottles of 100 and 1000; Tablets ALDORIL®-25, containing 250 mg methyldopa and 25 mg hydrochlorothiazide, bottles of 100 and 1000; Tablets ALDORIL® D30, containing 500 mg methyldopa and 30 mg hydrochlorothiazide, bottles of 100; Tablets ALDORIL® D50, containing 500 mg methyldopa and 50 mg hydrochlorothiazide, bottles of 100.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486.

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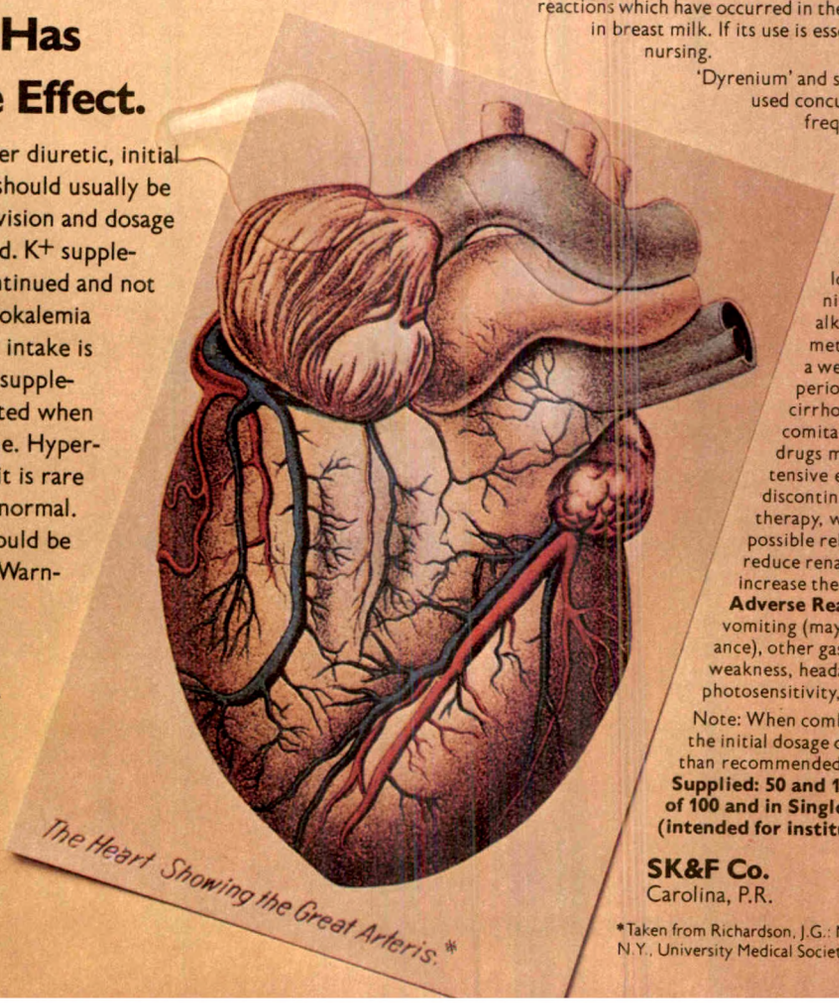
'Dyrenium' Has an Additive Effect.

When used with another diuretic, initial dosage of both agents should usually be reduced; careful supervision and dosage adjustment are required. K+ supplements should be discontinued and not reinstituted unless hypokalemia develops or dietary K+ intake is markedly reduced. K+ supplements are contraindicated when 'Dyrenium' is used alone. Hyperkalemia can occur, but it is rare when renal function is normal. Serum K+ and BUN should be checked regularly (see Warnings below).

1. Donaldson, E.K., et al.: *Brit. M.J.* 1:1254-5 (May 22) 1976.



*The Heart Showing the Great Arteris.**

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Contraindications: Anuria. Severe or progressive kidney disease or dysfunction. Severe hepatic disease. Pre-existing elevated serum potassium. Hypersensitivity. Continued use in developing hyperkalemia. Do not give potassium supplements, either by drug or by diet.

Warnings: Observe regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Check BUN and serum potassium periodically, especially in the elderly, diabetics, and those with suspected or confirmed renal insufficiency. Use in pregnancy requires weighing anticipated benefits against possible hazards to the fetus, including adverse reactions which have occurred in the adult. Triamterene may appear in breast milk. If its use is essential, the patient should stop nursing.

'Dyrenium' and spironolactone are not usually used concurrently; if they are, however, frequent serum potassium determinations are required.

Precautions: If hyperkalemia develops, withdraw the drug. The following may also occur: electrolyte imbalance, low-salt syndrome (with low salt intake), reversible mild nitrogen retention, decreasing alkali reserve with possible metabolic acidosis. Triamterene is a weak folic acid antagonist. Do periodic hematologic studies in cirrhotics with splenomegaly. Concomitant use with antihypertensive drugs may result in an additive hypotensive effect. When 'Dyrenium' is to be discontinued after intensive or prolonged therapy, withdraw gradually because of possible rebound kaliuresis. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Diarrhea, nausea and vomiting (may indicate electrolyte imbalance), other gastrointestinal disturbances, weakness, headache, dry mouth, anaphylaxis, photosensitivity, elevated uric acid, rash.

Note: When combined with another diuretic, the initial dosage of each agent should be lower than recommended.

Supplied: 50 and 100 mg. capsules, in bottles of 100 and in Single Unit Packages of 100 (intended for institutional use only).

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*Taken from Richardson, J.G.: Medicology, N.Y., University Medical Society, 1906.

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DESCRIPTION: *Klorvess Effervescent Granules:* Each packet (2.8 g) contains 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, L-lysine monohydrochloride 0.913 g in a sodium-, sugar- and carbohydrate-free effervescent formulation. Dissolution of the packet contents in water provides the potassium and chloride available for oral ingestion as potassium chloride, potassium bicarbonate, potassium citrate and L-lysine monohydrochloride.

Klorvess (potassium chloride) 10% Liquid: Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

INDICATIONS: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

CONTRAINDICATIONS: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

PRECAUTIONS: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements. Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis. High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest. To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve the packet contents of *Klorvess Effervescent Granules* in 3 to 4 ounces of cold water, fruit juice or other liquid or dilute each tablespoonful of *Klorvess (potassium chloride) 10% Liquid* in 3 to 4 ounces of cold water. Both of these solutions should be ingested slowly with or immediately after meals.

ADVERSE REACTIONS: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts. The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest. The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

DOSAGE AND ADMINISTRATION: *Klorvess Effervescent Granules:* Adults—One packet completely dissolved 2 to 4 times daily depending upon the requirements of the patient.

Klorvess (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) completely diluted in cold water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating.

OVERDOSAGE: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

HOW SUPPLIED: *Klorvess Effervescent Granules*—packages of 30 packets (2.8 g each). *Klorvess (potassium chloride) 10% Liquid* (dark red)—as a cherry-with-pit flavored liquid in pint and gallon bottles. Klorvess Effervescent Granules and Liquid are also available in institutional packaging as follows: *Klorvess Effervescent Granules*—packages of 1000 packets; *Klorvess Liquid*—36 (3 x 12) x 4 oz Unit-of-Use bottles and 100 (4 x 25) x 15 ml Unit-Dose bottles.

(For complete details, please consult full prescribing information)

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*INDICATIONS—Based on a review of this drug by the National Academy of Science-National Research Council and/or other information. FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension.

ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg (2 tablets) three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy. Tablets of 25 mg

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VOLUME 44

NUMBER 6

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CLINICAL STUDIES

1035 Abnormal Technetium-99m Pyrophosphate Images in Unstable Angina: Ischemia Versus Infarction?

ALLAN S. JAFFE, MILTON S. KLEIN, BHARTI R. PATEL, BARRY A. SIEGEL and ROBERT ROBERTS

Comparison of technetium-99m pyrophosphate images with frequent determinations of plasma creatine kinease and MB isoenzyme (MB CK) activity in 116 patients hospitalized with unstable angina revealed agreement in 88 percent of patients, normal tests in 69 percent and abnormal tests indicating acute myocardial infarction in 19 percent. In the remaining 12 percent, the scans were abnormal but MB CK activity was normal. These results suggest that abnormal technetium-99m pyrophosphate images in patients with unstable angina generally indicate myocardial necrosis. This technique is a reliable diagnostic technique for evaluating patients with unstable angina pectoris. With both techniques it is possible to detect patients with myocardial necrosis who would not be recognized with conventional diagnostic methods.

1040 Idiopathic Hypertrophic Subaortic Stenosis: Evaluation of Anginal Symptoms With Thallium-201 Myocardial Imaging

KENNETH A. RUBIN, JOHN MORRISON, MARVIN B. PADNICK, ALAN J. BINDER, SALVATORE CHIARAMIDA, DONALD MARGOULEFF, VELLORE T. PADMANABHAN and STEPHEN J. GULOTTA

In 10 symptomatic patients with angina pectoris, normal coronary angiograms and idiopathic hypertrophic subaortic stenosis, stress thallium-201 myocardial perfusion imaging proved a more useful noninvasive technique than submaximal treadmill exercise testing in ruling out the presence of significant coronary artery disease in such patients. The presence of asymmetric septal thickening in itself did not produce abnormal scans. Imaging revealed no significant perfusion defects in 9 of the 10 patients, whereas 7 showed left ventricular hypertrophy with S-T abnormalities in the electrocardiogram and 1 of the 3 patients with a normal resting electrocardiogram had a significant exercise-induced S-T segment depression. In five of the seven patients substernal chest pain developed and required termination of exercise. The cause of chest pain in patients with idiopathic hypertrophic subaortic stenosis and normal coronary arteries remains obscure.

1046 Left Bundle Branch Block: Angiographic Segmental Wall Motion Abnormalities

R. SANDERS WILLIAMS, VICTOR S. BEHAR and ROBERT H. PETER

Biplane cineangiographic studies of left ventricular wall motion in 15 patients with left bundle branch block and no significant coronary artery disease or diffuse cardiomyopathies demonstrated severe abnormalities in 6 by qualitative wall motion analysis; abnormal wall motion along at least one hemiaxis was demonstrated in 10 of 12 patients by computer-assisted quantitative analysis. Such segmental wall motion abnormalities are common in patients with left bundle branch block, even in the absence of coronary artery disease or diffuse cardiomyopathies and may result from the abnormal sequence of ventricular activation rather than from myocardial fibrosis. The excellent clinical course of these patients over 6 months to 5 years (no deaths) contrasts sharply with the poorer prognosis of patients with left bundle branch block and coronary artery disease.

1050 Performance of the Failing and Nonfailing Right Ventricle of Patients With Pulmonary Hypertension

PAUL D. STEIN, HANI N. SABBAH, DANIEL T. ANBE and MARIO MARZILLI

Measurements of the hemodynamic performance of the right ventricle in 34 patients indicate that the contractile effort of the right ventricle may be normal in pulmonary hypertensive heart disease even when the right ventricle fails in a clinical sense. Consequently right ventricular failure may develop in such patients although the cardiac

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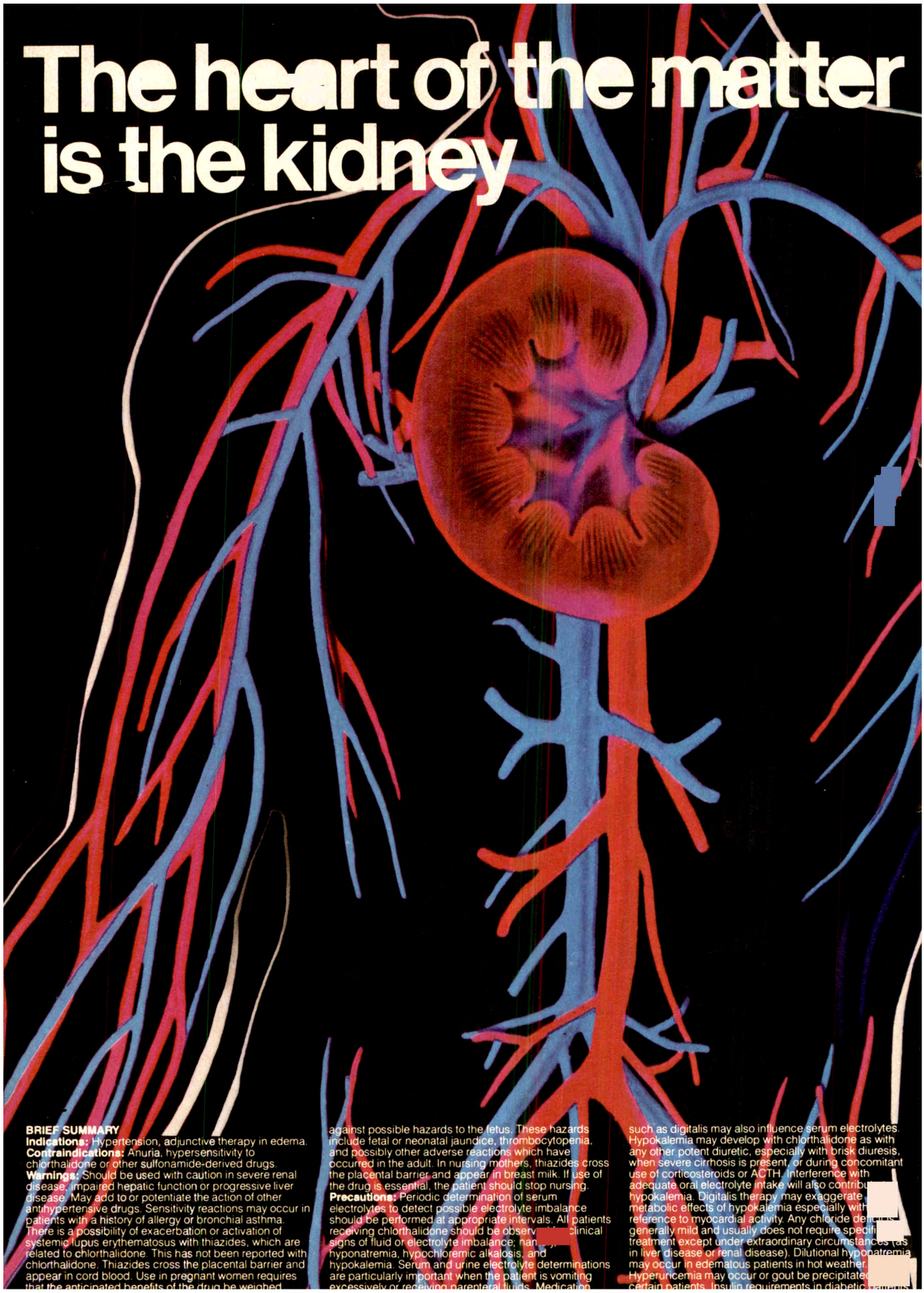
The heart of the matter is the kidney



BRIEF SUMMARY
Indications: Hypertension, adjunctive therapy in edema.
Contraindications: Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs.
Warnings: Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. There is a possibility of exacerbation or activation of systemic lupus erythematosus with thiazides, which are related to chlorthalidone. This has not been reported with chlorthalidone. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing.
Precautions: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate the metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients

in hypertension

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ay be increased, decreased, or unchanged and latent abetes mellitus may become manifest. Chlorthalidone d related drugs may increase the responsiveness to ocurarine. The antihypertensive effects of the drug ay be enhanced in the postsympathectomy patient lorthalidone and related drugs may decrease arterial sponsiveness to norepinephrine. If progressive renal pairment becomes evident, as indicated by a rising protein nitrogen or blood urea nitrogen, a careful ppraisal of therapy is necessary with consideration en to withholding or discontinuing diuretic therapy lorthalidone and related drugs may decrease serum levels without signs of thyroid disturbance **verse Reactions:** Anorexia, gastric irritation, nausea niting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn. **Usual Dose:** One tablet daily **How Supplied:** Tablets—100 mg. (white, scored), 50 mg. (aqua) and 25 mg. (peach) in bottles of 100 and 1000, unit-dose blister packs, boxes of 100 (10 x 10 strips). Also, 100 mg. and 50 mg. in PAKs of 28 tablets, boxes of 6

References: 1. Finnerty, F.A. Jr.: Managing Mild Hyp tension: A low-dose approach, Scientific Exhibit pres at Amer. Coll. Cardiol. 28th Annual Scientific Session Miami Beach, Fla., Mar. 11-15, 1979. **2.** Materson, B.J Dose response to chlorthalidone in patients with mild tension, Clin. Pharmacol. Ther. 24:192, 1978. **3.** Data USV Laboratories Inc.

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SUMMARY OF PRESCRIBING INFORMATION

* **Indications:** Based on a review of this drug by The National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"**Probably**" **effective:** The sublingual dosage form of SORBITRATE is indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: A history of sensitivity to the drug.

Warnings: Data supporting the use of nitrates during the early days of the acute phase of myocardial infarction are insufficient to establish safety.

Precautions: Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions: Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

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1056 Effect of Coronary Arterial Bypass Surgery on Exercise-Induced Ventricular Arrhythmias. Long-Term Follow-Up of a Prospective Randomized Study.

KENNETH L. LEHRMAN, ARA G. TILKIAN, HERBERT N. HULTGREN and ROBERT E. FOWLES

This study of 102 patients with stable angina pectoris shows that coronary bypass grafting decreases neither the frequency nor the severity of exercise-induced or resting ventricular arrhythmias. With the exception of exercise-induced ventricular tachycardia and fibrillation, no relation was found between ventricular arrhythmias and sudden death. These data suggest that exercise-induced ventricular arrhythmias may be related not to ischemia but to other effects of exercise such as cardiac stimulation by catecholamines or other factors. Exercise tests revealed a substantial improvement in performance in the surgically treated patients at 1 year compared with findings in the medically treated patients. This difference was still evident at 5 years but to a lesser degree.

1062 Detection of Left Ventricular Functional Reserve by Supine Exercise Hemodynamics in Patients With Severe, Chronic Heart Failure

HARRIS J. GELBERG, STANLEY A. RUBIN, THOMAS A. PORTS, BRUCE H. BRUNDAGE, WILLIAM W. PARMLEY and KANU CHATTERJEE

In this study of 20 patients with severe, chronic congestive heart failure maximal exercise increased the stroke work index in 8 and decreased it in 12 subjects. Despite these differences the groups could not be distinguished by the usual clinical criteria. At rest there were no clinical or hemodynamic differences between the groups. This study suggests that patients with severe heart failure demonstrate a spectrum of hemodynamic responses to exercise. Exercise hemodynamic determinations may be required to select appropriate therapy for heart failure and to evaluate the patient's ability to tolerate surgery.

1068 Relation Between the Precordial Projection of S-T Segment Changes After Exercise and Coronary Angiographic Findings

KIM M. FOX, ANDREW SELWYN, DAVID OAKLEY and JOHN P. SHILLINGFORD

In 100 patients subjected to diagnostic coronary arteriography and exercise testing the sensitivity of precordial electrocardiographic mapping (96 percent) for the diagnosis of coronary artery disease was significantly greater than that of the modified 12 lead electrocardiogram (80 percent). The specificity of the two lead systems was similar. Although there was no significant differences in the sensitivity (66 percent) and specificity (100 percent) of electrocardiographic mapping and of the 12 lead system in identifying three vessel disease, there was a significant difference in sensitivity (electrocardiographic mapping 74 percent, 12 lead system 42 percent) in identifying isolated single vessel disease. Electrocardiographic mapping provides additional information regarding the coronary arterial anatomy not available using the conventional 12 lead electrocardiogram.

1076 Hemodynamic Response to Exercise After Propranolol in Patients With Mitral Stenosis

GIUSEPPE GIUFFRIDA, GIULIO BONZANI, SANDRO BETOCCHI, FEDERICO PISCIONE, PIETRO GIUDICE, DOMENICO MICELI, FELICE MAZZA and MARIO CONDORELLI

This study suggests that propranolol may benefit patients with pure mitral stenosis, sinus rhythm and no cardiac failure when their symptoms occur during reversible conditions characterized by an increase in heart rate or cardiac output, or both. After a bolus injection of 5 mg of propranolol, the mean heart rate and cardiac index at rest were lower than during the control state, and during exercise the pulmonary wedge pressure and mitral valve gradient were lower than the control values in the 10 young patients studied. Left ventricular end-diastolic pressure and stroke index showed no significant changes. Inhibition of the tachycardia by propranolol during exercise seems to benefit patients with mitral stenosis.

Continued on page A19

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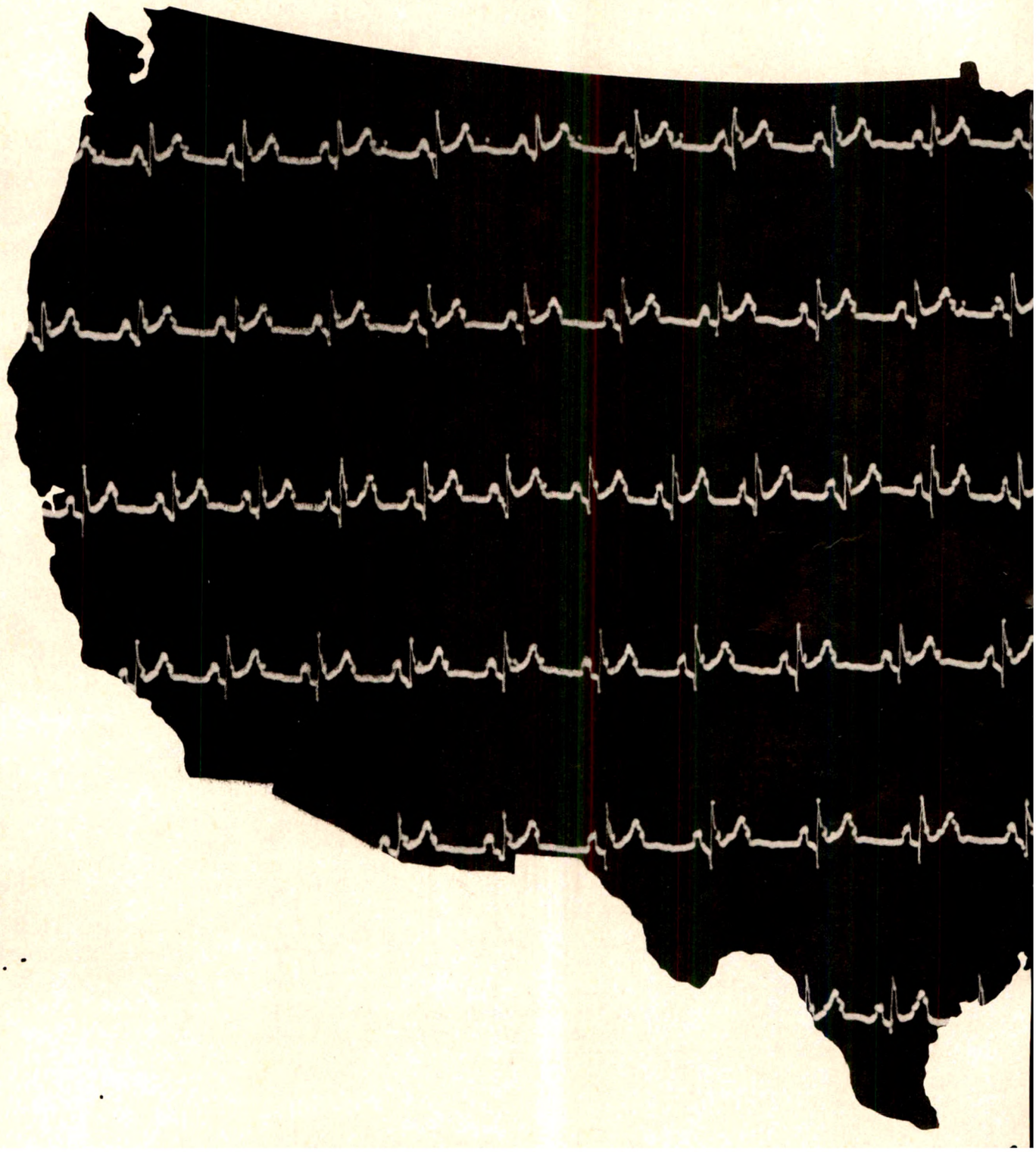

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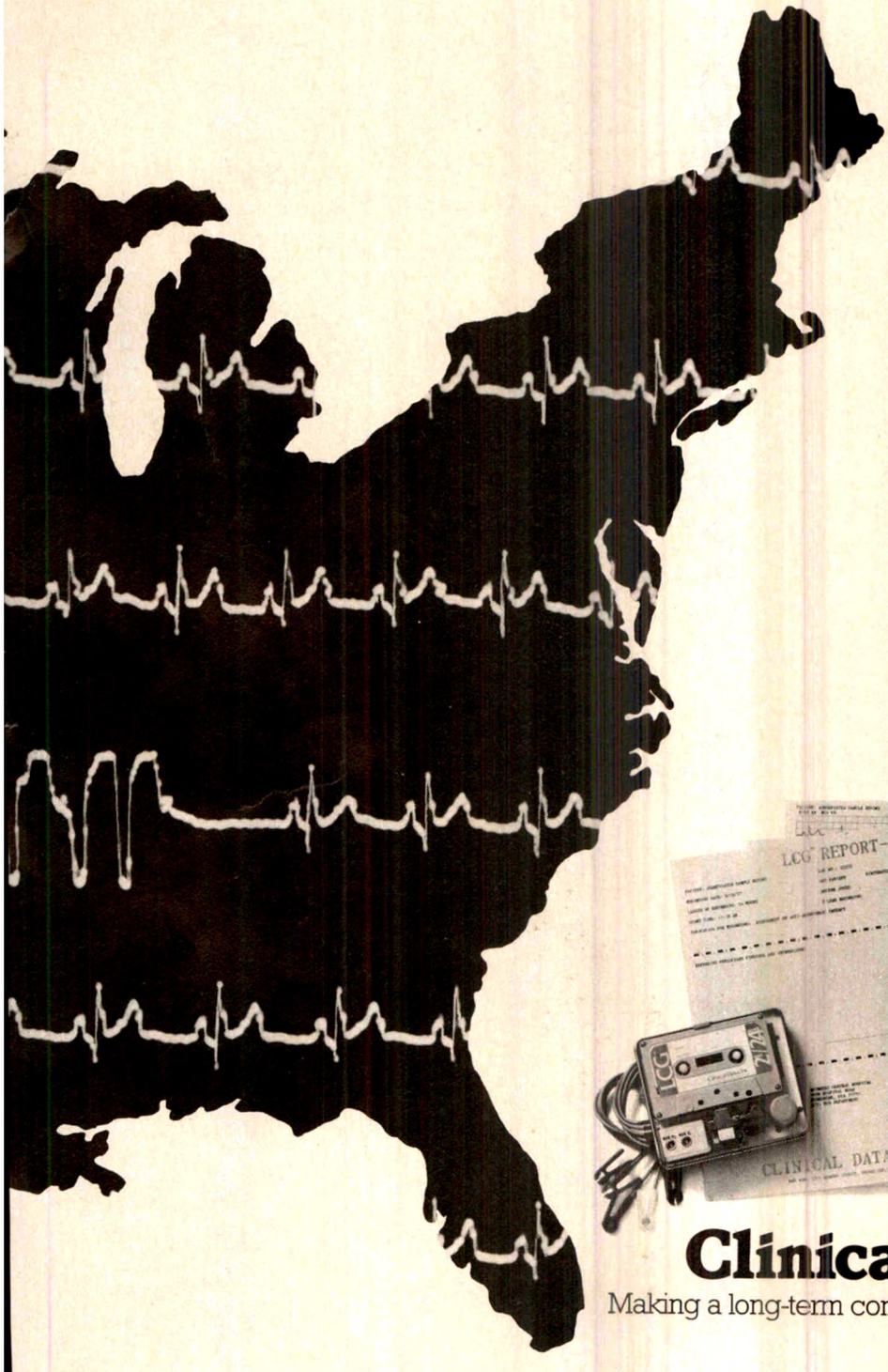

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1083 Histopathologic Correlates of Left Posterior Fascicular Block

JEAN-CLAUDE DEMOULIN and HENRI E. KULBERTUS

These observations on the histopathology in 13 cases of left posterior fascicular block demonstrate these alterations are less widely spread than in left anterior fascicular block, but more severe and more proximally located, involving the A-V ring and the upper part of the interventricular septum, and probably accounting for the poorer prognosis and easier progression to complete A-V block. Among the four patients with chronic left posterior block, three had heavy calcifications of the left side of the cardiac skeleton and one had diphtheritic myocarditis. In the nine patients with left posterior fascicular block related to myocardial infarction the coronary arterial lesions were very severe.

1089 Incidence, Determinants and Significance of Fixed Retrograde Conduction in the Region of the Atrioventricular Node. Evidence for Retrograde Atrioventricular Nodal Bypass Tracts

JOSEPH ANTHONY C. GOMES, MALKIAT S. DHATT, ANTHONY N. DAMATO, MASOOD AKHTAR and CAROL A. HOLDER

Eighteen of 104 consecutive patients (17 percent) in whom anterograde and retrograde electrophysiologic studies were performed demonstrated evidence (short and fixed H_2–A_2 intervals) for fixed and rapid retrograde conduction in the atrioventricular (A-V) nodal region. During intracardiac stimulation studies a large incidence of palpitations and the ability to induce either atrial echoes or paroxysmal supraventricular tachycardia during intracardiac stimulation studies were observed. Neither tachycardia nor ventricular echoes could be induced during retrograde studies. The presence of A-V nodal bypass tracts (intranodal or extranodal) functioning in retrograde manner could provide the substrate for the initiation and sustenance of reentrant supraventricular tachycardia in patients with the Wolff-Parkinson-White syndrome and in those with concealed ventriculoatrial bypass tracts functioning in retrograde manner.

1099 Reciprocal Tachycardias Using Accessory Pathways With Long Conduction Time

JERONIMO FARRÉ, DAVID ROSS, ISAAC WIENER, FRITS W. BÄR, EDUARD J. VANAGT and HEIN J. J. WELLENS

Three patients with reentrant tachycardia were found to have an accessory pathway with very long conduction times, longer than those over the atrioventricular nodal–His-Purkinje pathway. This accessory pathway was incorporated in the tachycardia circuit and was able to conduct in one direction only, in retrograde manner in two patients and in anterograde manner in the third patient. These data indicate that accessory pathways with long conduction times, either because of a long intracardiac pathway or slow conducting properties, or both, exist in the human heart and may be involved in reciprocating tachycardia as in these three patients.

1110 The Risk of Pericardiocentesis

BERT WONG, JAY MURPHY, C. JOSEPH CHANG, KHATAB HASSENEIN and MARVIN DUNN

The incidence of adverse complications was relatively small in this series of 52 pericardiocenteses between 1971 to 1978. Complications consisted of one death, one cardiac arrest, one aspiration of a subdiaphragmatic abscess and five ventricular punctures without adverse sequelae. Pericardiocentesis was usually successful when performed for suspected malignant pericardial effusion but often unsuccessful when performed for suspected hemopericardium. Although the risk of this procedure is low, proper selection of patients with consideration of the disease process and the preoperative identification of the amount and anatomic location of the pericardial fluid can further minimize it.

SPECIAL ARTICLE

1115 Oxygen Deprivation and Early Myocardial Contractile Failure: A Reassessment of the Possible Role of Adenosine Triphosphate

DAVID J. HEARSE

Using an isolated rat heart preparation and high speed freeze-clamping technique, these investigators demonstrated that a substantial decrease in myocardial adenosine triphosphate (ATP) and creatine phosphate content

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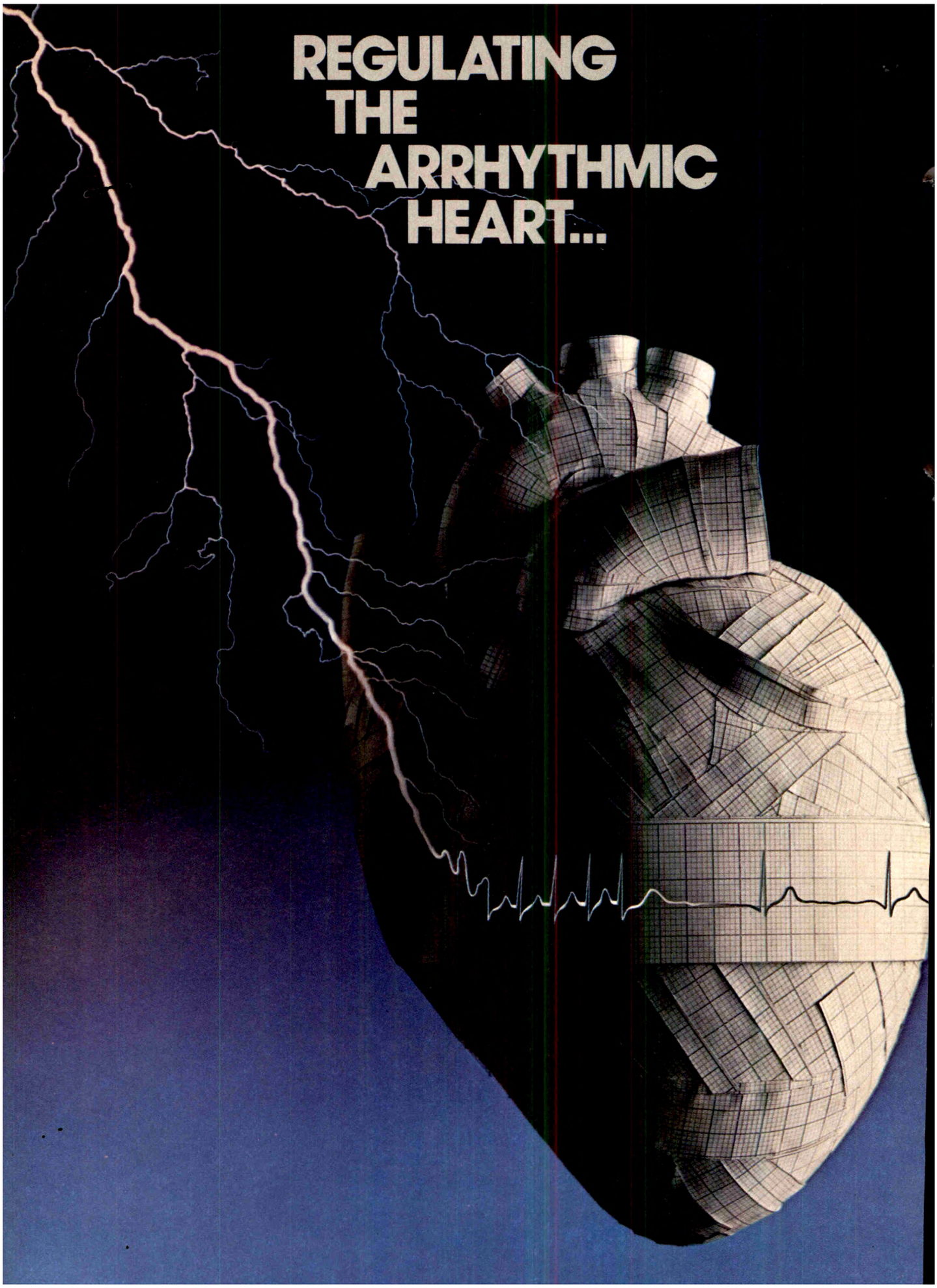
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ALONE Excessive exertions. Emotional upheavals. Anxieties. Stress. Catecholamines rise—atrial pacemakers overrespond. And the ECG reads PAT. Or persistent sinus tachycardia. Or persistent atrial extrasystoles. Consider INDERAL (propranolol HCl) alone. When conventional measures fail, a low 10 to 30 mg dose, given t.i.d. or q.i.d., will block cardiac beta-receptors from excessive catecholamine stimulation. Suppress ectopic pacemakers. And permit resumption of normal sinus rhythm. Even when normal sinus rhythm has not been restored, INDERAL slows conduction in the AV node and prolongs its refractory time. Slowed AV conduction will often block reentry circuits, to help restore sinus rhythm.

WITH The ECG reads atrial flutter. Or atrial fibrillation. You have digitalized your patient, but the arrhythmia is not yet controlled. Consider adding INDERAL (propranolol HCl). Combined with digitalis, it obviates increasing digitalis dosage to toxic levels—while slowing the ventricular rate sufficiently to achieve control. INDERAL also complements the action of other agents. Combined with quinidine, it allows lower doses of quinidine—reducing the need for toxic levels. And often, with INDERAL added, atrial arrhythmias respond when no single agent works alone.

INSTEAD The arrhythmia is induced by an antiarrhythmic drug such as digitalis or quinidine. Persists after discontinuance of the drug and correction of electrolyte imbalance. Consider INDERAL instead. Often the drug of choice, except in the presence of serious congestive heart failure. Often, too, INDERAL (propranolol HCl) abolishes supraventricular arrhythmias when either digitalis or quinidine has failed.

With proper patient selection—in the absence of contraindications such as bradycardia, greater than first degree heart block, asthma, and congestive heart failure unless failure is secondary to tachyarrhythmias treatable with INDERAL—serious cardiovascular and respiratory side effects are seldom encountered.* Rely on it: INDERAL. Alone. With. Or Instead.

*Please turn the page for brief summary of prescribing information on contraindications, adverse reactions, and warnings, including avoidance of abrupt withdrawal.

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Inderal® BRAND OF propranolol hydrochloride **A beta-adrenergic blocking agent**

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

ACTIONS: INDERAL is a beta-adrenergic receptor blocking drug, possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available beta receptor sites. When access to beta receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

Propranolol is almost completely absorbed from the gastrointestinal tract, but a portion is immediately bound by the liver. Peak effect occurs in one to one and one-half hours. The biologic half-life is approximately two to three hours. Propranolol is not significantly dialyzable. There is no simple correlation between dose or plasma level and therapeutic effect, and the dose-sensitivity range as observed in clinical practice is wide. The principal reason for this is that sympathetic tone varies widely between individuals. Since there is no reliable test to estimate sympathetic tone or to determine whether total beta blockade has been achieved, proper dosage requires titration.

Beta receptor blockade is useful in conditions in which, because of pathologic or functional changes, sympathetic activity is excessive or inappropriate and detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

The proper objective of beta blockade therapy is to decrease adverse sympathetic stimulation but not to the degree that may impair necessary sympathetic support.

Propranolol exerts its antiarrhythmic effects in concentrations associated with beta-adrenergic blockade and this appears to be its principal antiarrhythmic mechanism of action. The membrane effect also plays a role, particularly, some authorities believe, in digitalis-induced arrhythmias.

Beta-adrenergic blockade is of unique importance in the management of arrhythmias due to increased levels of circulating catecholamines or enhanced sensitivity of the heart to catecholamines (arrhythmias associated with pheochromocytoma, thyrotoxicosis, exercise).

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential and depresses cardiac function.

Propranolol may reduce the oxygen requirement of the heart at any given level of effort by blocking catecholamine-induced increases in heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. On the other hand, propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure, and systolic ejection period.

If the net physiologic effect of beta-adrenergic blockade in angina is advantageous, it would be expected to manifest itself during exercise by delayed onset of pain due to decreased oxygen requirement.

INDICATIONS: Cardiac Arrhythmias: *1.) Supraventricular arrhythmias:* a) Paroxysmal atrial tachycardias, particularly those arrhythmias induced by catecholamines or digitalis or associated with the Wolff-Parkinson-White syndrome. (See W-P-W under WARNINGS.) b) Persistent sinus tachycardia which is noncompensatory and impairs the well-being of the patient. c) Tachycardias and arrhythmias due to thyrotoxicosis when causing distress or increased hazard and when immediate effect is necessary as adjunctive, short term (2-4 weeks) therapy. May be used with, but not in place of, specific therapy. (See Thyrotoxicosis under WARNINGS.) d) Persistent atrial extrasystoles which impair the well-being of the patient and do not respond to conventional measures. e) Atrial flutter and fibrillation when ventricular rate cannot be controlled by digitalis alone, or when digitalis is contraindicated.

2.) Ventricular tachycardias: Ventricular arrhythmias do not respond to propranolol as predictably as do the supraventricular arrhythmias. a) Ventricular tachycardias: With the exception of those induced by catecholamines or digitalis, INDERAL is not the drug of first choice. In critical situations when cardioversion technics or other drugs are not indicated or are not effective, INDERAL may be considered. If, after consideration of the risks involved, INDERAL is used, it should be given intravenously in low dosage and very slowly. (See DOSAGE AND ADMINISTRATION.) *Care in the administration of* INDERAL *with constant electrocardiographic monitoring is essential as the failing heart requires some sympathetic drive for maintenance of myocardial tone.* b) Persistent premature ventricular extrasystoles which do not respond to conventional measures and impair the well-being of the patient.

3.) Tachyarrhythmias of digitalis intoxication: If digitalis-induced tachyarrhythmias persist following discontinuance of digitalis and correction of electrolyte abnormalities, they are usually reversible with *oral* INDERAL. Severe bradycardia may occur. (See OVERDOSAGE OR EXAGGERATED RESPONSE.)

Intravenous propranolol hydrochloride is reserved for life-threatening arrhythmias. Temporary maintenance with oral therapy may be indicated. (See DOSAGE AND ADMINISTRATION.)

4.) Resistant tachyarrhythmias due to excessive catecholamine action during anesthesia. Tachyarrhythmias due to excessive catecholamine action during anesthesia may sometimes arise because of release of endogenous catecholamines or administration of catecholamines. When usual measures fail in such arrhythmias, INDERAL may be given intravenously to abolish them. All general inhalation anesthetics produce some degree of myocardial depression. Therefore, when INDERAL is used to treat arrhythmias during anesthesia, it should be used with extreme caution and constant ECG and central venous pressure monitoring. (See WARNINGS.)

Hypertrophic Subaortic Stenosis: INDERAL is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL also improves exercise performance. The effectiveness of INDERAL in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta receptor stimulation. Clinical improvement may be temporary.

Pheochromocytoma: After primary treatment with an alpha-adrenergic blocking agent has been instituted, INDERAL may be useful as *adjunctive* therapy if the control of tachycardia becomes necessary before or during surgery.

It is hazardous to use INDERAL unless alpha-adrenergic blocking drugs are already in use, since this would predispose to serious blood pressure elevation. Blocking only the peripheral dilator (beta) action of epinephrine leaves its constrictor (alpha) action unopposed.

In the event of hemorrhage or shock, there is a disadvantage in having both beta and alpha blockade since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.

With inoperable or metastatic pheochromocytoma, INDERAL may be useful as an adjunct to the management of symptoms due to excessive beta receptor stimulation.

CONTRAINDICATIONS: INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS: CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (i.e., that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by INDERAL's negative inotropic effect. The effects of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, INDERAL therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.*, isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose.

PRECAUTIONS: Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS: *Cardiovascular:* bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory: bronchospasm

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DOSAGE AND ADMINISTRATION: The dosage range for INDERAL is different for each indication.

ORAL

ARRHYTHMIAS—10-30 mg three or four times daily, before meals and at bedtime.

HYPERTROPHIC SUBAORTIC STENOSIS—20-40 mg three or four times daily, before meals and at bedtime.

PHEOCHROMOCYTOMA—*Preoperatively*—60 mg daily in divided doses for three days prior to surgery, concomitantly with an alpha-adrenergic blocking agent.—*Management of inoperable tumor*—30 mg daily in divided doses.

PEDIATRIC DOSAGE At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

INTRAVENOUS Intravenous administration is reserved for life-threatening arrhythmias or those occurring under anesthesia. The usual dose is from 1 to 3 mg administered under careful monitoring, *e.g.* electrocardiographic, central venous pressure. The rate of administration should not exceed 1 mg (1 ml) per minute to diminish the possibility of lowering blood pressure and causing cardiac standstill. Sufficient time should be allowed for the drug to reach the site of action even when a slow circulation is present. If necessary, a second dose may be given after two minutes. Thereafter, additional drug should not be given in less than four hours. Additional INDERAL should not be given when the desired alteration in rate and/or rhythm is achieved.

Transference to oral therapy should be made as soon as possible.

The intravenous administration of INDERAL has not been evaluated adequately in the management of hypertensive emergencies.

OVERDOSAGE OR EXAGGERATED RESPONSE: IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg): IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY.

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS.

HYPOTENSION—VASOPRESSORS, *e.g.* LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE.)

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE.

HOW SUPPLIED: INDERAL (propranolol hydrochloride)

TABLETS: *No. 461*—Each scored tablet contains 10 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100. *No. 462*—Each scored tablet contains 20 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100. *No. 464*—Each scored tablet contains 40 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100. *No. 468*—Each scored tablet contains 80 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

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occurs after the onset of anoxia but before the onset of contractile failure. During the first 5 seconds of anoxia, contractile activity remains constant but ATP decreases by 25 percent and creatine phosphate by 50 percent. Contractile failure occurs and the rate of utilization of high energy phosphate declines with the cell content at a plateau or possibly increasing. These results suggest that ATP depletion in a specific cell compartment may be the primary trigger for early contractile failure. Whether the rapid, complex and interrelated exchange and breakdown of ATP and creatine phosphate during the first 10 seconds of anoxia is proton-generating or proton-consuming remains unsettled.

PEDIATRIC CARDIOLOGY

1122 Straddling and Overriding Atrioventricular Valves: Morphology and Classification

SIMCHA MILO, SIEW YEN HO, FERGUS J. MACARTNEY, JAMES L. WILKINSON, ANTON E. BECKER, ARNOLD C. G. WENINK, ADRIANA C. GITTENBERGER DE GROOT and ROBERT H. ANDERSON

This study of 57 hearts in which the orifice or tension apparatus of an atrioventricular (A-V) valve was related to both sides of a septum in the ventricular mass shows that such overriding or straddling valves can be easily categorized into four basic groups if attention is paid to the A-V connection and the morphologic features and relations of the ventricular chambers. The position of the connecting nodal tissue depended on whether the septum extended to the crux, anterior systems being found when it did not and either anterior or regular systems when it did, the latter variation depending on the A-V connection present. The recognition of these patterns has important surgical implications because the disposition of the conduction tissues varies with the pattern of straddling valve. Surgical options and risks to the conduction system are governed by these patterns.

1135 Positional Abnormalities of Atrioventricular Valves in Transposition of the Great Arteries Including Double Outlet Right Ventricle. Atrioventricular Valve Straddling and Malattachment

KALIM U. AZIZ, MILTON H. PAUL, ALEXANDER J. MUSTER and FAROUK S. IDRISS

The following two main types of positional abnormalities of the atrioventricular (A-V) valves were identified in this study of 10 patients with transposition of the great arteries including double outlet right ventricle. (1) Anular straddling in which the A-V anulus straddled the ventricular septum above the contralateral ventricle together with ventricular leaflet malattachment, and (2) leaflet malattachment of either the septal or ventricular type without significant straddling of the valve anulus. Angiography and sector scan echocardiography helped to identify these abnormalities of the A-V valves which are relevant to the surgical correlation of the complicated forms of transposition of the great arteries.

1146 Two Dimensional Echocardiographic Characteristics of Double Outlet Right Ventricle

THOMAS G. DiSESSA, ARTHUR D. HAGAN, CHARLES POPE, LINDA SAMTOY and WILLIAM F. FRIEDMAN

Real time, two dimensional echocardiographic studies in 46 patients with anomalies of the great vessels, including 13 children with double outlet right ventricle, proved diagnostic of double outlet right ventricle in all 13 and accurately differentiated this malformation from other anomalies of the great vessels. The relative ease of establishing atrioventricular valve-semilunar valve discontinuity with cross-sectional echocardiography substantiates the superiority of this form of tomographic imaging over M mode echocardiography in demonstrating this anatomic phenomenon. Two dimensional cardiac ultrasonic imaging may be expected to play an important role in selecting the most appropriate angiographic cross sections prior to hemodynamic and angiographic study.

1155 Pulsed Doppler Echocardiographic Detection of Total Anomalous Pulmonary Venous Return: Resolution of Left Atrial Line

JAMES GEOFFREY STEVENSON, ISAMU KAWABORI and WARREN G. GUNTHEROTH

In 33 infants pulsed Doppler echocardiography proved a useful technique for the resolution of left atrial lines noted on M mode echocardiography. With this technique five patients whose blood flow characteristics were different on either side of the left atrial line were found to have total anomalous pulmonary venous return at cardiac catheterization. In these patients the pulsed Doppler examination also identified a persistent left superior vena cava. In the remaining infants with identical blood flow characteristics on either side of the line, cardiac catheterization excluded total anomalous pulmonary venous return and cor triatriatum. The Doppler examination must be performed with care and may require that the precordial transducer position be lower than normal to determine direction of flow in an anomalous venous channel.

Continued on page A29

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A.	Total no. copies printed (Net Press Run)	25,419	25,600
B.	Paid circulation		
	1. Sales through dealers and carriers, street vendors and counter sales	—	—
	2. Mail subscriptions	23,665	24,093
C.	Total paid circulation (Sum of 10B1 and 10B2)	23,665	24,093
D.	Free distribution by mail, carrier or other means, samples, complimentary, and other free copies	1,245	915
E.	Total distribution (Sum of C and D)	24,910	25,008
F.	Copies not distributed		
	1. Office use, left over, unaccounted, spoiled after printing	509	592
	2. Returns from news agents	—	—
G.	Total (Sum of E, F1 and 2—should equal net press run shown in A)	25,419	25,600

11. I certify that the statements made by me above are correct and complete.

(Signature) Robert T. Brawn, Publisher

12. For completion by publishers mailing at the regular rates (Section 132.121, Postal Service Manual) 39 U. S. C. 3626 provides in pertinent part: "No person who would have been entitled to mail matter under former section 4359 of this title shall mail such matter at the rates provided under this subsection unless he files annually with the Postal Service a written request for permission to mail matter at such rates." In accordance with the provisions of this statute, I hereby request permission to mail the publication named in Item 1 at the phased postage rates presently authorized by 39 U. S. C. 3626.

(Signature) Robert T. Brawn, Publisher

NITROSTAT®
(nitroglycerin tablets, USP)

INDICATIONS
Nitrostat is indicated for the prophylaxis, treatment and management of patients with angina pectoris.

CONTRAINDICATIONS
Sublingual nitroglycerin therapy is contraindicated in patients with early myocardial infarction, severe anemia, increased intracranial pressure, and those with a known hypersensitivity to nitroglycerin.

PRECAUTIONS
Only the smallest dose required for effective relief of the acute anginal attack should be used. Excessive use may lead to the development of tolerance. Nitrostat tablets are intended for sublingual or buccal administration and should not be swallowed. The drug should be discontinued if blurring of vision or drying of the mouth occurs. Excessive dosage of nitroglycerin may produce severe headaches.

ADVERSE REACTIONS
Transient headache may occur immediately after use. Vertigo, weakness, palpitation, and other manifestations of postural hypotension may develop occasionally, particularly in erect, immobile patients. Syncope due to nitrate vasodilation has been reported. Alcohol may accentuate the cerebral ischemia symptoms.

METHOD OF ADMINISTRATION
One tablet should be dissolved under the tongue or in the buccal pouch at the first sign of an acute anginal attack. The dose may be repeated approximately every five minutes until relief is obtained. Nitrostat may be used prophylactically five to ten minutes prior to engaging in activities which might precipitate an acute attack.

HOW SUPPLIED
Nitrostat is supplied in four strengths in bottles containing 100 tablets each, with color-coded labels, and in color-coded Patient Convenience Packages of four bottles of 25 tablets each.
0.15 mg (1/400 grain): N 0071-0568-24 [06]—Ctn. of 10 bottles of 100 tablets; N 0071-0568-13—Convenience Package.
0.3 mg (1/200 grain): N 0071-0569-24 [06]—Ctn. of 10 bottles of 100 tablets; N 0071-0569-13—Convenience Package.
0.4 mg (1/150 grain): N 0071-0570-24 [06]—Ctn. of 10 bottles of 100 tablets; N 0071-0570-13—Convenience Package.
0.6 mg (1/100 grain): N 0071-0571-24 [06]—Ctn. of 10 bottles of 100 tablets; N 0071-0571-13—Convenience Package. **YF**

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Morris Plains, NJ 07950 USA

PD-JA-2810-1-P (7-79)

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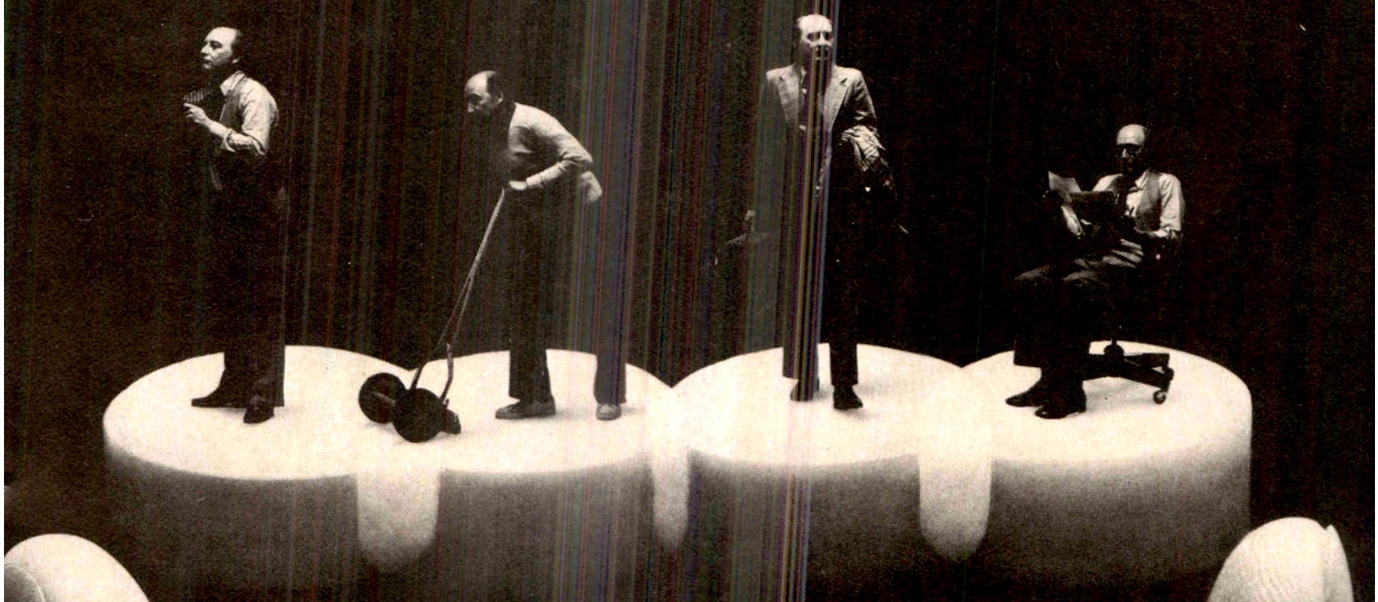
(nitroglycerin tablets, USP)

4x25s



☐ allows your patient to store one bottle of Nitrostat 25s for immediate use at four different locations

☐ is more stable than conventional nitroglycerin tablets

☐ has an average assay better than 100% of label claim for at least 60 months after manufacture*

☐ is useful as sole therapy; is useful as concomitant therapy with long-acting nitrates and/or propranolol hydrochloride

*Five-year expiration date when stored at recommended conditions in an unopened bottle.
Data on file, Parke-Davis.

Please see preceding page for brief summary of prescribing information.

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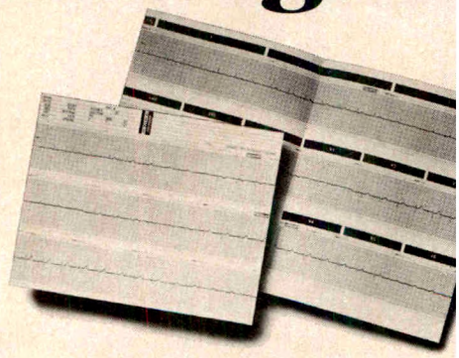

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BURDICK

A concern for cardiac ca

CONTENTS

1159 Increased Systemic Vascular Resistance in Neonates With Pulmonary Hypertension

JAY M. MILSTEIN, BOYD W. GOETZMAN, THOMAS A. RIEMENSCHNEIDER and RICHARD P. WENNBERG

Neonates with pulmonary hypertension have a prolonged aortic diastolic half-life (the time necessary for the aortic diastolic pressure to decrease to 50 percent of an initially selected value after dissipation of the dicrotic notch [T1/2]). Such patients with pulmonary hypertension also have increased systemic vascular resistance. T1/2, prolonged in patients with pulmonary hypertension and right to left ductus arteriosus shunting, is even more prolonged in patients with pulmonary hypertension without evidence of shunting, indicating that the total resistance in this group is even greater. The vasoconstriction responsible for the increased systemic vascular resistance in the patients was probably compensatory rather than primary since most of them did not have elevated systemic blood pressure. Aortic diastolic pressure analysis may provide an important tool for assessing systemic vascular resistance or both systemic and pulmonary vascular resistance in the presence of a patent ductus arteriosus.

STUDIES IN HYPERTENSION

1163 Volume Studies in Men With Mild to Moderate Hypertension

JOHN H. BAUER and CHARLES S. BROOKS

In comparison with age-matched control subjects, patients with normal renin hypertension display similar body fluid characteristics, but have an increase in the intracellular fluid and a significantly depressed ratio of extracellular fluid to total body water due to either a redistribution of salt and water from the extracellular fluid into the intracellular fluid or an excess accumulation of salt and water in the intracellular fluid. No volume differences were found between subjects with low renin hypertension and age-matched subjects with normal renin hypertension. Subjects with low renin hypertension cannot therefore be distinguished from those with normal renin hypertension by any unique volume disorder. The suppressed renin state in these patients is probably unrelated to volume excess.

REPORTS ON THERAPY

1171 Surgery for Life-Threatening Ventricular Tachyarrhythmias

ANDREW J. BUDA, EDWARD B. STINSON and DONALD C. HARRISON

Left ventricular aneurysmectomy without mapping techniques for refractory life-threatening ventricular arrhythmias in 49 patients produced a satisfactory clinical result in the majority of long-term survivors of the operation. The operative mortality rate was 19.6 percent in this group. High risk variables included recent myocardial infarction (60 percent mortality rate), coronary bypass grafting without myocardial resection and an elevated left ventricular end-diastolic pressure. Although resection of ventricular arrhythmias stopped the life-threatening ventricular tachycardia and fibrillation, ambulatory electrocardiographic monitoring demonstrated that ventricular premature complexes still occurred. Twenty of the 35 long-term survivors remain on antiarrhythmic medications; 15 do not require them. Additional study is necessary to identify subgroups of patients with refractory life-threatening arrhythmias who need mapping.

1178 Development of Pharmacodynamic Tolerance to Prazosin in Congestive Heart Failure

CHRISTOPHER E. DESCH, RAYMOND D. MAGORIEN, DOUGLAS W. TRIFFON, MARVIN F. BLANFORD, DONALD V. UNVERFERTH and CARL V. LEIER

Central and regional hemodynamic measurements in seven patients with severe low output heart failure showed that a single 5 mg oral dose of prazosin significantly increased the cardiac index and stroke volume index while significantly decreasing systemic, pulmonary and pulmonary capillary wedge pressures and vascular resistances. Striking attenuation of these hemodynamic changes occurred when the same dose was administered to seven other patients after 24 hours of pretreatment with oral prazosin, 2 mg every 8 hours. These results suggest that the development of pharmacodynamic tolerance may limit the usefulness of this vasodilator as a preload and afterload reducing agent in chronic congestive heart failure. The mechanism for the development of this pharmacodynamic tolerance is not known at present. Increasing the dose of prazosin will not necessarily prevent the attenuation.

Continued on page A33

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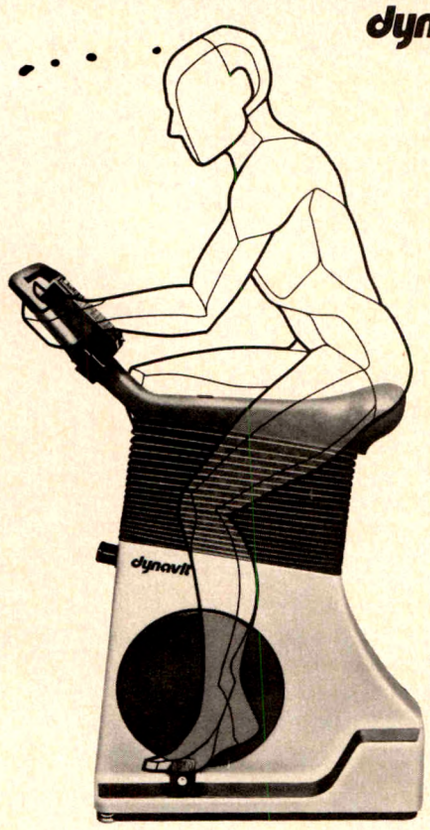

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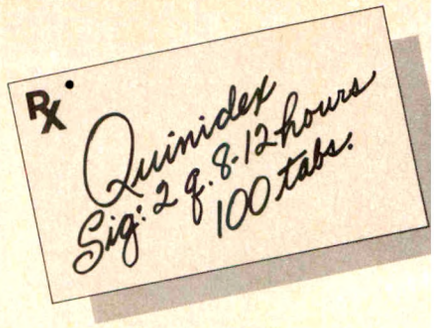

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INDICATIONS: Premature atrial and ventricular contractions, paroxysmal atrial tachycardia, paroxysmal A-V junctional rhythm, atrial flutter, paroxysmal atrial fibrillation, established atrial fibrillation when therapy is appropriate, paroxysmal ventricular tachycardia when not associated with complete heartblock, maintenance therapy after electrical conversion of atrial fibrillation and/or flutter.
CONTRAINDICATIONS: Intraventricular conduction defects. A-V block. Idiosyncrasy or hypersensitivity. Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine.
WARNING: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio and resulting extremely rapid ventricular rate.
PRECAUTIONS: All the precautions applying to regular quinidine therapy apply to the Extentab form. Use with care in patients with severe congestive failure, renal insufficiency or with digitalis intoxication.

Patients should be carefully observed for signs of toxicity: e.g., (1) allergy or idiosyncrasy, such as febrile reactions, skin eruptions, and thrombocytopenia (extremely rare); (2) "cinchonism," such as tinnitus, blurred vision, dizziness, lightheadedness, and tremor; (3) G-I symptoms (nausea, vomiting, diarrhea, and colic); (4) cardiotoxic effects such as ventricular extrasystoles occurring at a rate of one or more every 6 normal beats, an increase of the QRS complex of 50% or more, a complete A-V block, or ventricular tachycardia.
NOTE: The development of "cinchonism" is not usually sufficient reason for terminating quinidine therapy. G-I symptoms can also be minimized by giving the drug with food.
ADVERSE REACTIONS: Cases of quinidine-induced hypoprothrombinemic hemorrhage in patients on chronic anticoagulant drug therapy have been reported.
DOSAGE: Two Quinidex Extentabs every 8 to 12 hours.
HOW SUPPLIED: White sugar-coated Extentabs in bottles of 100 and 250 (NDC 0031-6649).

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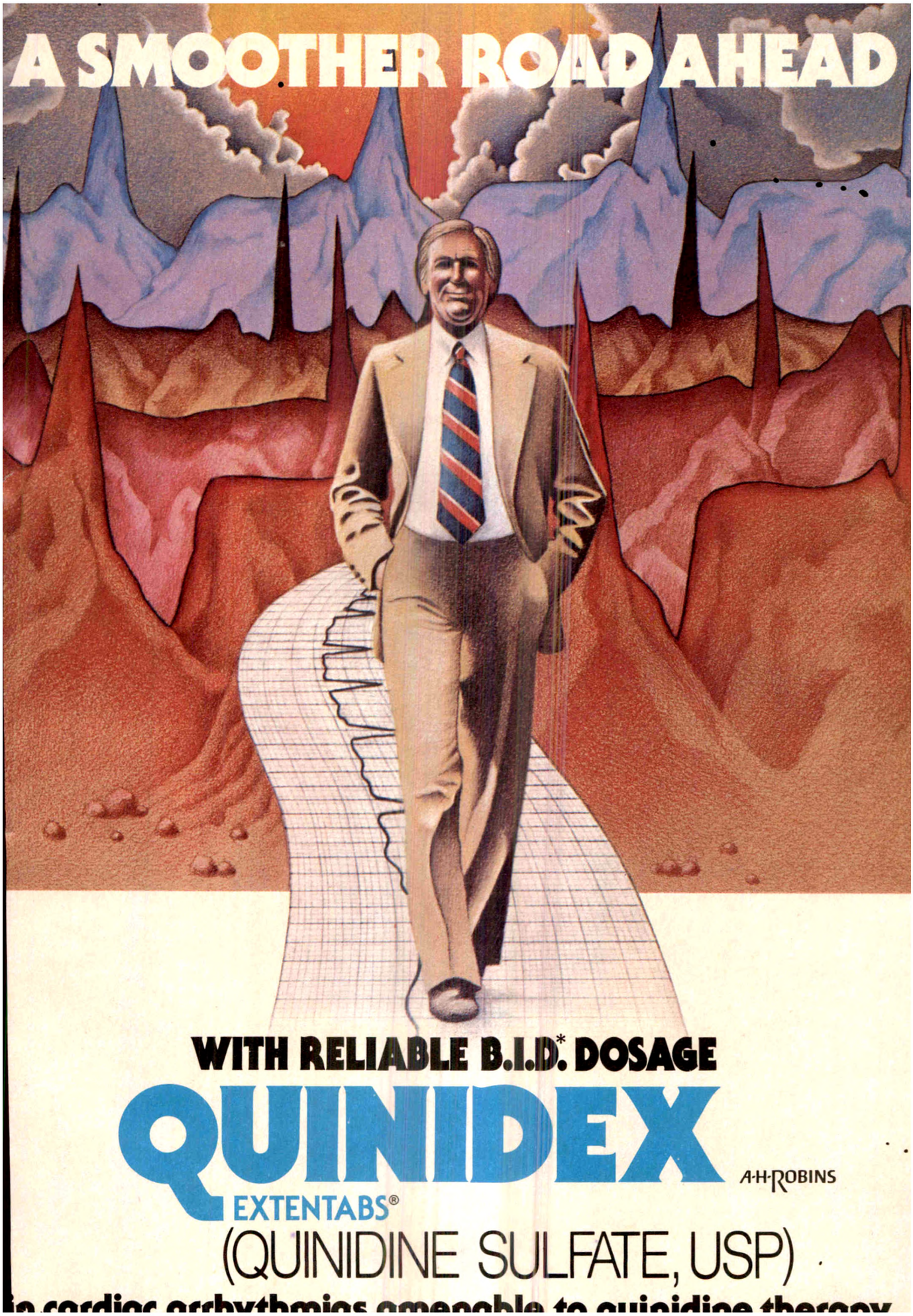

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1183 Influence of Short-Term Oral Hydralazine Therapy on Exercise Hemodynamics in Patients With Severe Chronic Heart Failure

STANLEY A. RUBIN, KANU CHATTERJEE, THOMAS A. PORTS, HARRIS J. GELBERG, BRUCE H. BRUNDAGE and WILLIAM W. PARMLEY

In this evaluation of 14 patients with severe chronic heart failure conventional therapy increased the cardiac output from 3.4 ± 0.8 at rest to 4.7 ± 1.4 liters/min during exercise mainly by an increase in heart rate. After the addition of hydralazine the cardiac output at rest increased to 5.0 ± 1.4 liters at rest to 6.0 ± 1.8 liters/min at peak exercise because of an increase in stroke volume that was maintained during exercise. There was also an increase (47 percent) in cardiac output and a decrease (−35 percent) in systemic vascular resistance. Despite improved cardiac performance after hydralazine, there was little or no increase in oxygen consumption or in the maximal exercise capacity of patients with chronic heart failure. Increased cardiac output and stroke volume with similar changes in left ventricular filling pressure during exercise indicated improved left ventricular performance after hydralazine therapy. Clinical follow-up 2 months after long-term therapy revealed subjective improvement in exercise tolerance in 13 of the 14 patients.

1190 Pharmacokinetics of Digoxin in Patients With Acute Myocardial Infarction

ULLA R. KORHONEN, ANTTI J. JOUNELA, ARTO J. PAKARINEN, PERTTI J. PENTIKÄINEN and JUHA T. TAKKUNEN

After oral administration of digoxin (0.75 mg) to 12 patients with left-sided cardiac failure due to acute myocardial infarction, the absorption of oral digoxin was slower and the peak concentration remained lower in these subjects than in 9 healthy control subjects. The total amount of digoxin absorbed was unchanged. The delayed absorption may be due to decreased gastrointestinal motility, increased sympathetic activity and decreased mesenteric blood flow. These results indicate that the total dosage of digoxin need not be modified in patients with acute myocardial infarction and left ventricular failure, minor but clinically relevant changes may occur in the pharmacokinetics of a single oral dose, and the retarded absorption of oral digoxin may delay the clinical response of these patients.

1195 Hemodynamic Effects of Intravenous Metoprolol

PATRICK D. BOURDILLON, RUDOLPH CANEPA-ANSON and ANTHONY F. RICKARDS

In this hemodynamic study of 10 patients undergoing routine cardiac catheterization the beta adrenergic blocking effect of intravenous metoprolol was confirmed by a 53 percent reduction in the heart rate response to an isoproterenol challenge and by a significant 48 percent decrease in the change of the first derivative of left ventricular pressure (dP/dt) with the combination of atrial pacing and isoproterenol. These responses were obtained without significant alterations in ejection fraction, preload or afterload. Analysis of segmental wall motion before and after metoprolol reveals only minor beneficial changes in a small proportion of patients with coronary artery disease. No significant alterations occurred in synchronicity or mechanical efficiency of the left ventricle. In clinical use at the dose given the main cardiac depressant action will result from the blockade of increased sympathetic activity.

DIAGNOSTIC SHELF

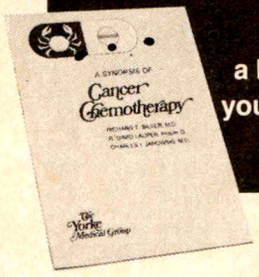
1201 Selective Coronary Arteriography in Congenitally Corrected Transposition of the Great Arteries

PEDER M. SHEA, JERRE F. LUTZ, WALTER V. R. VIEWEG, FRANCIS H. CORCORAN, RICHARD VAN PRAAGH and THOMAS J. HOUGEN

As illustrated by these three cases of congenitally corrected transposition of the great arteries, the angiographic characteristics of the epicardial coronary arterial pattern may permit accurate identification of the ventricles in complex congenital heart disease with poorly defined intraventricular morphologic features. In these cases the morphologic features of the epicardial coronary anatomy were distinctive and identifiable angiographically as morphologically right and left coronary arteries specifically concordant with the morphologically right and left ventricles. The consistent relation of the distal coronary anatomic pattern with the morphologic features of the ventricle supports the theory of a dual embryologic origin of the coronary arteries.

Continued on page A36

How to Keep Up with Drug Interaction in Cancer Chemotherapy



Three authorities from a leading medical center show you how to use the most current chemotherapeutic agents

A SYNOPSIS OF Cancer Chemotherapy

At last a way to keep up with the bewildering proliferation of new chemotherapeutic drugs which have come into use relatively recently. This just published guide will be valuable to every hospital, and every oncology specialist, general internist, clinical pharmacist, and nurse oncologist.

A SYNOPSIS OF CANCER CHEMOTHERAPY is a concise, readily understandable "how to" manual. Developed originally for staff use at The New York Hospital-Cornell Medical Center, the concept proved so successful it was decided to make it available to other professionals. The new users of the SYNOPSIS have the advantage of a proven, time-tested learning system. It is written in a unique, compact work-book style to keep reading time to a minimum.

The reader can quickly find the following for both commercially available and investigational drugs:

- Structure
- Mechanism of Action
- Pharmacokinetics
- Toxicity
- Therapy
- Availability

The chemotherapeutic agents in the main listing section cover these categories:

- Alkylating Agents
- Antimetabolites
- Mitotic Inhibitors
- Antibiotics
- Miscellaneous (includes such drugs as Mithramycin, Mitotane, etc.)

RICHARD T. SILVER, MD, F.A.C.P., F.A.B.C.O.
Chief, Oncology Service, Div. Hematology-Oncology, Clinical Professor of Medicine, Cornell University Medical College, Attending Physician, New York Hospital, Exec. Officer, Cancer & Leukemia Group B.

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Brief Summary of Prescribing Information

Indications and Usage: Symptomatic relief of anxiety, tension, agitation, irritability a insomnia associated with anxiety neuroses and transient situational disturbances; anxie associated with depressive symptoms and as a treatment of symptoms of anxiety if such sym toms are a significant feature of functional or organic disorders, particularly gastrointestinal cardiovascular.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by syste atic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CN acting drugs, warn patients on lorazepam not to operate machinery or motor vehicles, and diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with bar turates and alcohol have occurred following abrupt discontinuance of benzodiazepin (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Adc tion-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillan when on benzodiazepines because of their predisposition to habituation and dependenc Withdrawal symptoms have also been reported following abrupt discontinuance of benzo azepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid ov sedation.

Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occ sional convulsions.

Observe usual precautions with impaired renal or hepatic function.

Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepa has not been shown of significant benefit in treating gastrointestinal or cardiovascular comp nent.

Esophageal dilation occurred in rats treated with lorazepam for more than 1 year 6mg/kg/day. No effect dose was 1.25mg/kg/day (approximately 6 times the maximum hum therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn wit 2 months of first observation. Clinical significance is unknown; but use of lorazepam for p longed periods and in geriatric patients requires caution and frequent monitoring for sympto of upper G.I. disease.

Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have h elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function te are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depress effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabb Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschi malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship dosage. Although all these anomalies were not present in the concurrent control group, th have been reported to occur randomly in historical controls. At 40mg/kg and higher, there w evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lo doses. Clinical significance of these findings is not known. However, increased risk of conge tal malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam a meprobamate) during first trimester of pregnancy has been suggested in several studi Because use of these drugs is rarely a matter of urgency, use of lorazepam during this per should almost always be avoided. Possibility that a woman of child-bearing potential may pregnant at institution of therapy should be considered. Advise patients if they become pr nant to communicate with their physician about desirability of discontinuing the drug.

In humans, blood levels from umbilical cord blood indicate placental transfer of lorazep and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like ot benzodiazepines. As a general rule, nursing should not be undertaken while on a drug sir many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and gener disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxic patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9 weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, n sea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, function disturbance, various gastrointestinal symptoms and autonomic manifestations. Ir dence of sedation and unsteadiness increased with age. Small decreases in blood press have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind that multiple age may have been taken. Manifestations of overdosage include somnolence, confusion and cor Induce vomiting and/or undertake gastric lavage followed by general supportive care, monit ing of vital signs and close observation. Hypotension, though unlikely, usually may be control with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® (lorazepam) IV for Anxiety

Dosage: **Individualize for maximum beneficial effects. Increase do gradually when needed, giving higher evening dose before increasi daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosa may vary from 1 to 10mg/day in divided doses. For elderly or deb tated, initially 1-2mg/day; insomnia due to anxiety or transient situ tional stress, 2-4mg h.s.**

How Supplied: **0.5, 1.0 and 2.0mg tablets.**

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Philadelphia, PA 19101
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The anxious heart.

Since anxiety so often accompanies cardiovascular disease, you may wish to institute adjunctive therapy to help bring this complicating factor under control.

Seven benzodiazepines are now at your disposal. All of them are anxiolytics. One of them—Ativan (lorazepam)—has been specifically evaluated in seven double-blind, controlled studies involving 423 patients (211 on Ativan) and found significantly effective in the relief of anxiety associated with organic and functional cardiovascular disorders. The cardiovascular component has not, of course, been shown to be significantly benefited by such therapy.

In addition to this outstanding record of clinical usefulness, Ativan offers you a unique pharmacokinetic profile. Unlike older benzodiazepines, it does not generate multiple active metabolites; steady-state serum levels are rapidly achieved and disappear rapidly once you decide to discontinue therapy. (The pharmacokinetic profile of a drug can define such characteristics as absorption, distribution, metabolism and elimination but cannot, at present, be directly related to its therapeutic effectiveness.)

Compatible with cardiotonics, antihypertensives, diuretics, anticoagulants and nonnarcotic analgesics*...usually well tolerated...simple to use on a b.i.d. schedule...a preferred prescription to control anxiety in cardiovascular disease.

*No evidence of any clinically significant interaction between Ativan and any other medication given concomitantly was observed in clinical studies. All benzodiazepines, however, including Ativan, produce added CNS depressant effects when administered with alcohol and other CNS depressants.

See important information on preceding page.

Ativan® (IV) for Anxiety

(lorazepam)

CONTENTS

1207 Two Dimensional Echocardiography in Differentiating Right Atrial and Tricuspid Valve Mass Lesions
PATRICIA C. COME, GEORGE S. KURLAND and HUGH S. VINE

As illustrated in four cases, the characteristic M mode echocardiographic pattern of a mass of echoes appearing, with a lag phase, beneath the anterior leaflet of the mitral or tricuspid valve in diastole is not necessarily specific for an atrial tumor. Differentiation of leaflet vegetation from an atrial mass prolapsing through the tricuspid valve was not possible with M mode scanning alone. In these cases the two dimensional echocardiogram proved helpful in confirming the presence or absence of a right-sided mass in the heart and in defining more precisely the location of the echocardiographic density relative to the right atrium and tricuspid valve.

EDITORIALS

1213 How Should Refractory Ventricular Tachycardia Be Treated?
JOHN A. KASTOR

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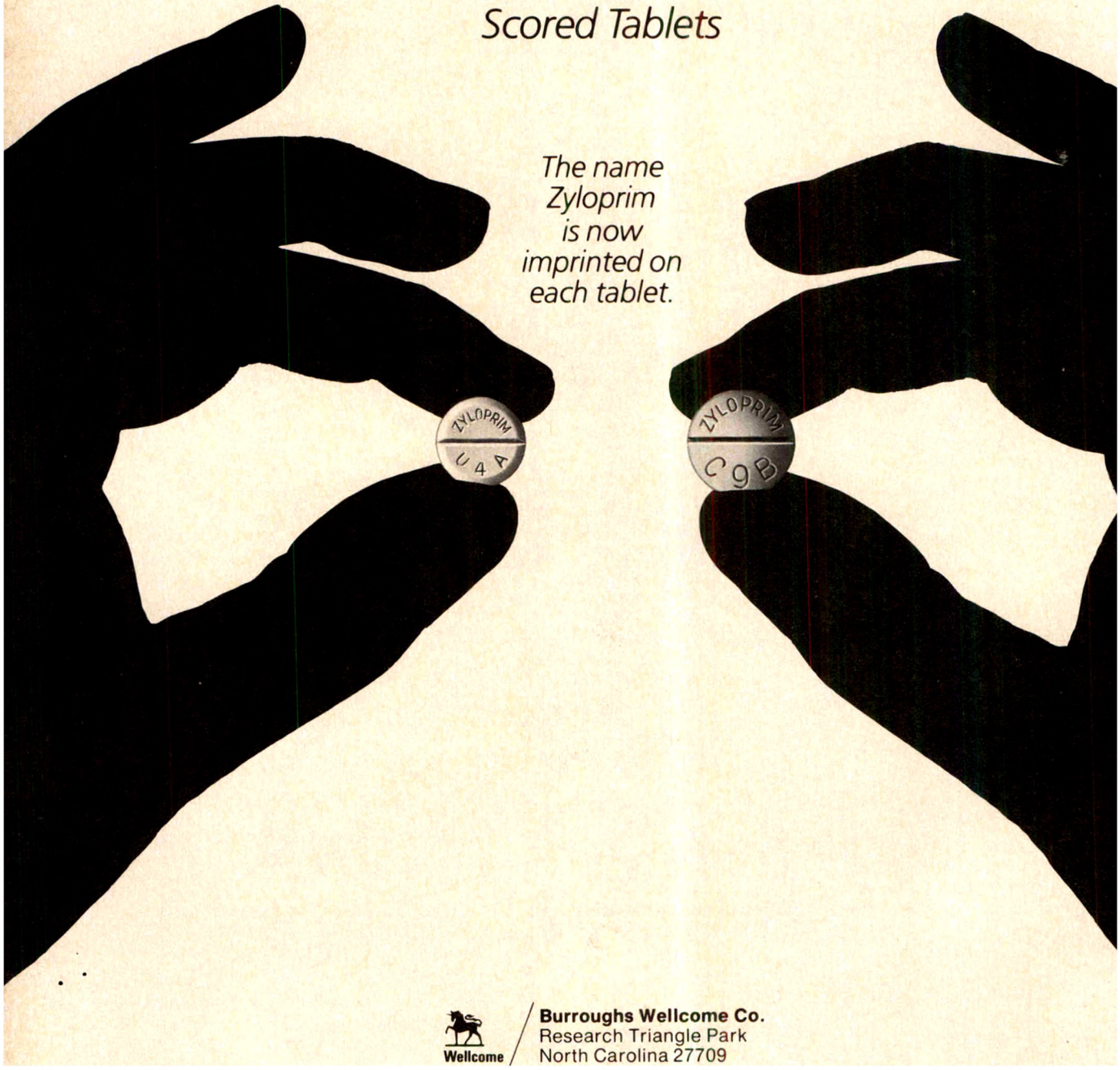

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CLINICAL STUDIES

Abnormal Technetium-99m Pyrophosphate Images in Unstable Angina: Ischemia Versus Infarction?

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There is controversy concerning the specificity of myocardial infarc imaging with technetium-99m pyrophosphate due to the high frequenc of false positive images, especially in patients with unstable angina. I this study technetium-99m pyrophosphate images were compared wit frequent determinations of plasma creatine kinase, MB isoenzyme (MI CK) activity in 116 patients admitted with the diagnosis of unstable angina It was hypothesized that frequent measurement of MB CK activity, sensitive and specific marker for myocardial necrosis, using sensitiv assay techniques would detect small amounts of myocardial necrosi which might have been unrecognized by conventional clinical methods The scintigraphic results and isoenzyme determinations agreed in 8 percent of patients; both tests were normal in 69 percent and both were abnormal, indicating acute myocardial infarction, in 19 percent of patients In the remaining 14 patients (12 percent), the scans were abnormal, bu MB CK activity was normal. In five of these patients (4 percent), abnorma scintigrams presumably reflected persistent scan positivity after previous myocardial infarction. Only the remaining nine patients (8 percent) coul be classified as having unexplained false positive scans, a frequency substantially less than that reported by other investigators who based the diagnosis of myocardial infarction on conventional clinical criteria. These results suggest that abnormal technetium-99m pyrophosphate images in patients with unstable angina generally indicate myocardial ne- crosis.

Myocardial infarct scintigraphy with technetium-99m pyrophosphate is a valuable adjunct in the diagnosis of acute myocardial infarction. However, there is a continuing controversy concerning the specificity of this technique for detecting acute, irreversible myocardial injury.[1-3] Experimentally injured myocardium avidly accumulates technetium-99m pyrophosphate; this phenomenon appears related, both anatomically and temporally, to the deposition within necrotic cells of amorphous calcium phosphate and crystalline hydroxyapatite.[4] In contrast, clinical studies provide less clear results and suggest that myocardial uptake of technetium-99m pyrophosphate may occur with ischemia alone. This has been particularly true in patients with unstable angina pectoris; fa

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Previous studies of myocardial infarct scintigraphy in unstable angina evaluated the results of this test in relation to conventional diagnostic criteria for acute myocardial necrosis (that is, electrocardiographic and plasma enzymatic changes). However, these studies have not included measurements of plasma creatine kinase, MB isoenzyme (MB CK) activity at frequent intervals using highly sensitive assay methods and, thus, may not have correctly detected patients with myocardial necrosis accompanied by only slight, transient elevations in plasma enzyme activity. To determine whether some of the abnormal technetium-99m pyrophosphate images observed in unstable angina are related to small regions of acute myocardial necrosis, we obtained both scintigrams and frequent, sensitive measurements of plasma MB CK activity in patients with clinically diagnosed unstable angina.

Methods

Study patients: Patients with a clinical diagnosis of unstable angina were selected for this study. This diagnosis was based on a history of recent onset of angina occurring at rest or at night or exhibiting a marked change in duration, frequency or intensity. Serial electrocardiograms were reviewed and classified as normal or as demonstrating S-T segment elevation or S-T segment depression alone, S-T segment and T wave abnormalities or T wave abnormalities alone. Patients whose electrocardiogram demonstrated new Q waves while they were in the coronary care unit were excluded from the study. During the period from January 1974 to June 1976, a total of 266 patients met these criteria and were enrolled consecutively. Myocardial infarct scintigrams with technetium-99m pyrophosphate were obtained in 116 of these patients. There were 67 men and 49 women with a mean age of 58 years (range 32 to 91 years). Thirty-five patients gave a history of prior myocardial infarction. None of the 116 patients had disorders known to be associated with false positive technetium-99m pyrophosphate images (for example, thoracic trauma, lung tumor, recent cardioversion, calcified valves, ventricular aneurysm or cardiomyopathy).

Radionuclide studies: Myocardial images were obtained 2 to 4 hours after the intravenous administration of 15 mCi of technetium-99m pyrophosphate. The studies were performed 48 to 72 hours after admission to the coronary care unit. Images were obtained in the anterior, right and left anterior oblique and left lateral projections using a scintillation camera fitted with a low energy, medium resolution collimator. The scintigrams were interpreted by a single experienced observer who had no knowledge of the clinical history. The intensity of myocardial tracer uptake was graded as described by Berman et al.,[9] except that uptake of 2+ intensity or greater was considered abnormal whether it was focal or diffuse. Because the 2+ diffuse pattern has been the one most often associated with apparent false positive images, our classification of this subset as abnormal was expected to maximize the number of false positive results.[2,9]

Plasma enzyme analyses: During the first 24 to 36 hours after admission, blood samples from a peripheral vein were obtained through an indwelling heparin lock every 6 to 12 hours for the determination of total plasma creatine kinase (CK) and MB CK activity. Total plasma CK activity was measured with the Rosalki method.[10] In our laboratory, 75 U/liter is considered the upper limit of the normal range.

TABLE 1

Technetium-99m Pyrophosphate Imaging: Comparison With MB CK Determinations

Imaging Result	MB CK Result	Patients no.	Patients %	Comment
Normal	Normal	80	69	True negative
Abnormal	Abnormal	22	19	True positive
Abnormal	Normal	5	4	Prior myocardial infarction
Abnormal	Normal	9	8	False positive

metric method which reliably detects a plasma level of less than 1 IU/liter.[11] Samples were assayed with and without creatine phosphate, the specific substrate for creatine kinase, to detect false positive reactions due to fluorescence of adenylate kinase. Normal levels of plasma MB CK activity range from 0 to 5 IU/liter, the mean being 1.5 ± 0.6 IU/liter. Plasma MB CK activity greater than 5 IU/liter was considered abnormal and indicative of myocardial necrosis.[11,12]

Results

Patients with normal scintigrams: The scintigraphic and enzymatic results are compared in Table I. No patient in the study group had elevated plasma MB CK activity and a normal technetium-99m pyrophosphate image. Eighty patients (69 percent of the total patient group) had normal technetium-99m pyrophosphate images and normal MB CK activity. The electrocardiograms were normal in 55 of these patients and demonstrated S-T segment elevation in 7, S-T segment and T wave abnormalities in 9, T wave abnormalities alone in 7 and left bundle branch block in 2. Although 10 of these patients had elevations in total plasma CK activity, serially determined plasma MB CK activity was consistently less than 5 IU/liter. These patients were thought not to have had a myocardial infarction.

Patients with abnormal scintigrams: Technetium-99m pyrophosphate images were abnormal in 36 patients (31 percent); this frequency of abnormal scintigrams in patients with unstable angina is similar to that reported by others.[3,5–8] Serial electrocardiograms were normal in 6 of these patients and demonstrated S-T segment elevation in 11, S-T segment and T wave abnormalities in 10, T wave abnormalities alone in 3 and S-T segment depression alone in 6.

Of the 36 patients with abnormal images, 22 had elevated total plasma CK and MB CK activity. In these 22 patients, the images demonstrated focal accumulation in 21 and diffuse tracer uptake in 1. Focally increased activity was localized to the anterior wall of the left ventricle in 16 patients and to the inferior wall in 5.

A typical MB CK time-activity curve from one of our patients is shown in Figure 1. MB CK activity peaks approximately 12 hours after infarction (or about 8 hours after the initial rise of MB CK activity) and returns to baseline within 20 hours. In 7 of 22 patients, plasma MB CK activity had returned to normal by 18 hours and, in an additional 6 patients, it had returned

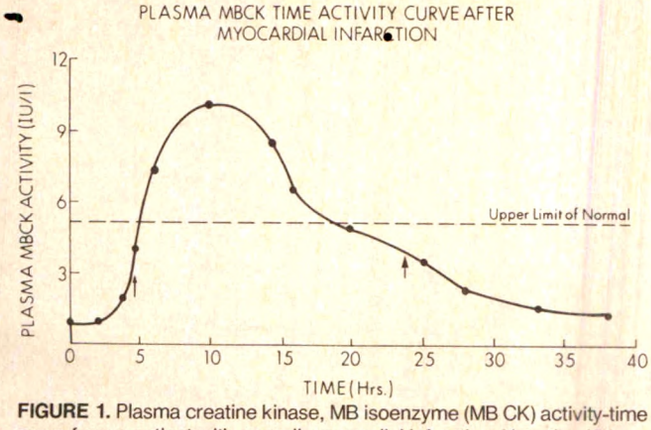

FIGURE 1. Plasma creatine kinase, MB isoenzyme (MB CK) activity-time curve from a patient with a small myocardial infarction. Note the 15 hour interval during which MB CK determinations are elevated. Had plasma samples been obtained at the times designated by the arrows, enzymatic criteria for the diagnosis of myocardial infarction would not be fulfilled. IU/L = international units per liter.

Abnormal scans with normal MB CK activity: Fourteen patients had abnormal technetium-99m pyrophosphate images and normal plasma MB-CK activity; two of these patients had elevated total plasma CK activity. In 12 patients, the images demonstrated focal uptake (anterior in 8, inferior in 4) and, in the remaining 2, there was diffuse uptake. Five of the patients with focal abnormalities had a documented transmural myocardial infarction within the preceding year (within 6 months in three patients). Abnormal tracer accumulation, which is presumably due to continuing ischemic injury and myocytolysis, may still occur several months after transmural myocardial infarction.[13,14] We believe that this phenomenon explains the abnormal scans in these five patients. Thus, only 9 of the 116 patients (8 percent) had unexplained abnormal technetium-99m pyrophosphate images with normal plasma MB CK activity. We consider these patients to have apparent false positive scintigrams.

Discussion

Sensitivity and specificity of myocardial infarct scintigraphy in unstable angina: In this investigation, we performed frequent determinations of plasma creatine kinase (MB CK) activity in patients with unstable angina pectoris. When this technique is used to define patients with acute myocardial infarction, the frequency of unexplained false positive technetium-99m pyrophosphate scintigrams (8 percent) is substantially less than that reported by others.[3,5–8] Our results (Table II) indicate that technetium-99m pyrophosphate imaging is a reliable diagnostic technique for evaluating patients with unstable angina pectoris. Because none of our patients had a normal technetium-99m pyrophosphate scintigram and elevated plasma MB CK activity, both the test sensitivity and the predictive value of a negative scan were 100 percent. In contrast to earlier reports, the test specificity (90 percent) and the predictive value (71 percent) of a positive scintigram were also high. Because patients with unstable angina commonly have had chest pain for several days, it is possible that elevated MB CK activity might have been found in some of the patients with apparent false positive scans if they had been admitted earlier to the hospital. This would improve both the specificity and positive predictive value of myocardial infarct scintigraphy.

TABLE II

Reliability of Technetium-99m Pyrophosphate Imaging in Unstable Angina

Sensitivity	= 22/22 = 100%
Specificity*	= 80/89 = 90%
Predictive value of negative image	= 80/80 = 100%
Predictive value of positive image*	= 22/31 = 71%

* The five patients who had abnormal images and normal MB CK determinations but who had had a prior myocardial infarction and were thought to have persistently abnormal scintigrams are excluded from this analysis. If these patients are included, the specificity decreases to 84 percent and the positive predictive value decreases to 61 percent.

Although our results differ from those of others,[3,5–8] it is unlikely that our criteria for image interpretation could explain the difference. Classification of images with 2+ diffuse tracer uptake as abnormal should have maximized sensitivity while potentially increasing the frequency of false positive results. That the former was accomplished is supported by the observation that no patient had a normal scan and an elevated plasma MB CK activity level.

The low frequency of false positive scintigrams and thus, the relatively high predictive value of a positive scan in our study most likely reflect the greater sensitivity of our enzymatic criteria compared with conventional techniques for the diagnosis of acute myocardial infarction. The explanation for the high sensitivity of our enzymatic criteria is the more frequent serial determinations of plasma MB CK activity and the use of a sensitive assay technique.

Sensitivity and specificity of plasma MB CK activity: In both closed and open chest dogs, we have shown[15] that elevated plasma MB CK activity is consistently associated with histologic evidence for myocardial necrosis. Conversely, transient coronary occlusion, insufficient to cause myocardial necrosis, does not elevate plasma MB CK activity.[15] In patients, plasma MB CK activity is not increased after uncomplicated cardiac catheterization or after thoracic, abdominal, genitourinary or orthopedic surgery since MB CK activity is undetectable in fresh human skeletal muscle, stomach, small and large intestine, brain, lung, liver, spleen and kidney.[11] Thus, plasma MB CK activity is a sensitive and highly specific marker for myocardial necrosis.

Most techniques for measuring plasma MB CK activity detect levels exceeding 5 to 10 IU/liter.[16] In contrast, the kinetic fluorometric assay used in this study reproducibly detects less than 1 IU/liter and thus identifies very small changes in plasma MB CK activi-

ty.[11] Elevations of plasma MB CK activity in patients such as the one presented in Figure 1 might be missed using conventional assays because this patient's peak MB CK was only 11 IU/liter. In addition, patients who present with unstable angina and have positive technetium-99m pyrophosphate images associated with small zones of necrosis may have abnormal levels of plasma MB CK activity for only a brief time. As can be seen in Figure 1, if plasma MB CK activity had been measured only at more conventional sampling intervals (for example, 5 and 20 hours), the results would have fallen within the normal range. In this study, the diagnosis of myocardial infarction might have been missed in as many as 13 of 22 patients (59 percent) if plasma MB CK activity had been assayed only at 24 hour intervals. The scintigrams in these patients would then have been classified as false positive.

Correlation with experimental and clinicopathologic data: Our results support the conclusions of several previous experimental and clinicopathologic studies that suggest that technetium-99m pyrophosphate uptake is specific for myocardial necrosis. Experimental studies[17] in cultured fetal mouse hearts indicate that technetium-99m pyrophosphate uptake is greatest in irreversibly injured myocardial cells. Buja et al.[4] reported that technetium-99m pyrophosphate accumulates only in regions with histologic evidence of necrosis and with myocardial calcium accumulation. The accumulation of technetium-99m pyrophosphate in necrotic myocardium appears to depend on the maintenance of at least some myocardial perfusion as assessed with the injection of microspheres.[18] In experimental myocardial infarction in dogs,[19] we showed a close correlation between myocardial necrosis determined morphometrically, depletion of myocardial CK isoenzyme, and the cardiac accumulation of technetium-99m pyrophosphate.

Clinical and pathologic studies further support the thesis that technetium-99m pyrophosphate accumulation is a specific indicator of myocardial necrosis. Scintigrams obtained in patients with angina and S-T segment depression at the time of stress testing have been consistently normal.[20,21] In a clinicopathologic study of 52 patients who had undergone myocardial infarct scintigraphy, Poliner et al.[22] found abnormal scans in 29 of 31 patients with "gross, obvious" myocardial infarction at autopsy. In five patients with unstable angina who had abnormal technetium-99m pyrophosphate images and in seven patients with "persistently positive scintigrams," there was evidence of irreversible myocardial damage with myocytolysis, coagulation necrosis or fibrosis.

Despite these findings, previous clinical studies of technetium-99m pyrophosphate imaging have been less conclusive. Wynne et al.[2] compiled the results of 15 studies and reported an overall frequency of false positive images of 17 percent in 1,083 patients without clinical evidence of acute myocardial infarction. An even higher frequency of false positive images (up to 42 percent) was reported in patients with unstable angina.[3,5–8] Our results suggest that most abnormal technetium-99m pyrophosphate scintigrams in patients with unstable angina are truly indicative of acute myocardial necrosis. However, the extent of myocardial injury is often slight and thus this injury is unlikely to be detected by conventional clinical methods, but will be recognized only if plasma MB CK activity is frequently assayed with sensitive techniques.

Clinical implications: Our study was not designed to evaluate the relative utility of myocardial infarct scintigraphy and measurements of MB CK activity for the diagnosis of acute myocardial infarction in patients with unstable angina. However, our results suggest that with both techniques it is possible to detect patients with myocardial necrosis who would not be recognized with conventional diagnostic methods. In addition, it is possible that technetium-99m pyrophosphate imaging may provide the only evidence of infarction in some patients, particularly those who are admitted to the hospital after plasma MB CK activity has returned to normal levels. The prognostic significance of abnormal technetium-99m pyrophosphate scintigrams in patients with unstable angina (with and without corresponding alterations in plasma MB CK activity) warrants further study and may provide the best guidance concerning the appropriate use of this diagnostic technique.

When plasma MB CK activity is assayed on frequent serial samples with sensitive techniques, there is a close correspondence between abnormal technetium-99m pyrophosphate scans and elevated levels of plasma MB CK. Our results, in contrast to those of previous clinical investigations, indicate that abnormal technetium-99m pyrophosphate scintigrams in patients with unstable angina generally reflect myocardial necrosis.

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Idiopathic Hypertrophic Subaortic Stenosis: Evaluation of Anginal Symptoms With Thallium-201 Myocardial Imaging

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The evaluation of angina pectoris in patients with idiopathic hypertrophic subaortic stenosis is difficult in those in the age group prone to coronary artery disease. Ten patients with angina pectoris, normal coronary angiograms and idiopathic hypertrophic subaortic stenosis were studied with thallium-201 myocardial imaging performed in conjunction with submaximal treadmill exercise testing. The resting electrocardiogram demonstrated left ventricular hypertrophy with S-T segment abnormalities in seven patients, thereby vitiating the further increase in S-T segment abnormalities that developed in these patients during exercise or in the postexercise period. Of the three patients with a normal resting electrocardiogram, one had significant exercise-induced S-T segment depression. Thallium-201 myocardial imaging revealed no significant perfusion defects in 9 of the 10 patients (90 percent). In one patient with severe left ventricular hypertrophy significant perfusion defects developed after exercise that were not present at rest. Stress thallium-201 myocardial perfusion imaging is a useful noninvasive technique that assists in ruling out the presence of significant coronary artery disease in patients with idiopathic hypertrophic subaortic stenosis.

The coexistence of idiopathic hypertrophic subaortic stenosis and coronary arterial disease has been well documented over the past 6 years.[1–3] Although echocardiography has provided a reliable, noninvasive technique for confirming the clinical diagnosis of idiopathic hypertrophic subaortic stenosis,[4,5] the evaluation of anginal symptoms in these patients presents a diagnostic problem. Because resting electrocardiographic abnormalities, including left ventricular hypertrophy, are frequently present in these patients,[6,7] evaluation with exercise stress testing is often unreliable.[8] Cardiac catheterization and selective coronary angiography are usually necessary to establish the presence or absence of coronary artery disease.

Recent data suggest that stress thallium-201 myocardial perfusion scanning allows the estimation of regional myocardial blood flow to areas supplied by critically narrowed coronary arteries.[9–11] The present study was undertaken to evaluate the usefulness of stress myocardial perfusion imaging with thallium-201 in symptomatic patients with idiopathic hypertrophic subaortic stenosis and angina pectoris with angiographically normal coronary arteries.

Methods

Patients. The study group consisted of eight consecutive patients with typical exertional angina and two with atypical chest pain in whom the diagnosis of idiopathic hypertrophic subaortic stenosis was established with clinical, hemodynamic and echocardiographic evaluation. All 10 patients had angiographically normal coronary arteries. There were seven men and three women with a mean age of 54.9 years (range 17 to 63 years). Clinical and laboratory data on the 10 patients are summarized in Table I. All patients had transseptal left heart catheterization with the catheter carefully placed in the inflow tract to avoid the entrapment phenomenon. Gradients were induced or increased across

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TABLE I

Clinical Features and Diagnostic Results in 10 Patients

Case no.	Age (yr) & Sex	Symptoms	Echocardiogram		Cardiac Catheterization	
			SAM	IVS:LPW Ratio	Resting LVOF Gradient (mm Hg)	Provoked LVOF Gradient (mm Hg)
1	17M	Atypical chest pain	+	1.5:1	6	92
2	39F	Exertional chest pain; dizziness	+	3.5:1	0	60
3	50F	Chest pressure with shortness of breath	+	1.2:1	36	180
4	63M	Chest pressure; fatigue	+	1.8:1	60	NA
5	45M	Exertional chest pain	+	2.5:1	0	NA
6	48F	Exertional chest pain; shortness of breath	+	2:1	38	NA
7	53M	Exertional chest pain	+	1.8:1	10	50
8	62M	Exertional fatigue; chest pressure	+	2:1	88	192
9	63M	Chest pressure with shortness of breath	+	2.2:1	16	90
10	49M	Atypical chest pain; fatigue	0	1.5:1	0	20

IVS = interventricular septal thickness; LPW = left posterior wall thickness; LVOF = left ventricular outflow tract; NA = not attempted; SAM = systolic anterior movement of anterior mitral leaflet.

the left ventricular outflow tract in seven patients by inducing ventricular premature beats and recording the postextrasystolic beats or by having the patient perform the Valsalva maneuver or inhale amyl nitrite. Simultaneous left ventricular inflow and ascending aortic pressures were recorded to evaluate the change in pressure gradient across the left ventricular outflow tract. Simultaneous left ventricular inflow and outflow pressures demonstrated the obstruction to be subvalvular.

The echocardiographic criteria used for diagnosis of idiopathic hypertrophic subaortic stenosis were a septal-free wall index equal or greater than to 1.3, systolic anterior motion of the mitral valve, or both.

Coronary arteriography: Selective coronary arteriography was performed using the Sones technique. Exposures were made on 35 mm double-X negative Kodak film at 60 frames/sec using a GE DXS-550 9 inch (23 cm) and 6 inch (14 cm) single plane image intensifier system. Arteriograms were obtained in the anteroposterior and left and right anterior oblique views with hemiaxial views obtained for better visualization of the proximal left coronary system. Each study was reviewed by three independent observers.

Exercise testing: Treadmill exercise testing was performed in all 10 patients using a modified Balke technique. A scalp vein needle was inserted percutaneously into a forearm vein to facilitate injection of thallium-201 during exercise. Standard 12 lead electrocardiograms were recorded at rest and in the postexercise period using a Marquette 3000 Automatic Electrocardiograph. During exercise, leads V_4 to V_6 were recorded using an Avionics 3070 Electrocardiocharter with linear response characteristics throughout the range of 0.05 to 150 hertz which was fitted with a low noise stress cable.

After an initial warm-up period of 2 minutes during which the patient walked on the treadmill at a speed of 3 miles/hour and zero grade, the grade was increased by 2.5° every 2 minutes whereas the speed remained constant at 3 miles/hour. Exercise was terminated when the patient complained of chest pain or fatigue or when the preselected submaximal heart rate (85 percent of the maximal heart rate for age) was achieved. Thallium-201 chloride was injected at peak exercise, and patients were encouraged to maintain that level of exercise for an additional minute after administration of the radionuclide.

Myocardial perfusion imaging: Thallium-201 chloride was administered intravenously in a dose of 2 to 3 mCi during peak exercise. Myocardial perfusion imaging was begun within 10 minutes in all but one patient in whom imaging was begun within 20 minutes (Patient 2). Myocardial images were recorded in the anterior view, 15° and 45° left anterior oblique views, and left lateral view. A gamma scintillation camera (Searle Pho/Gamma LEM) interfaced with a DEC (Digital Equipment Corporation) PDP 11/35 computer was equipped with a low energy, high resolution converging collimator and images were recorded with a 20 percent window centered on the mercury X-ray peaks (69 to 80 kev). In each view 300,000 to 400,000 counts were collected and the data stored on a 64 by 64 matrix. The perfusion scintigrams were enhanced with a nine point computer smoothing technique before data analysis. With algorithms, the perimeter of the myocardial image was circumscribed in a regular region, and all cells outside of this region were changed to zero counts. The minimal count within the regular region circumscribing the left ventricle was considered as background and thus subtracted from each cell in the matrix.

With a regular region of interest algorithm, the left ventricular scintigrams were divided into seven equal squares drawn to fit the left ventricle on each view. Regions were not necessarily representative of a specific myocardial area but were chosen to evaluate possible subsegmental areas of diminished myocardial perfusion.

In each view, the region with the highest count density was used as a relative index of normal to compare with the other six regions. Counts in each region were subtracted from the region with the highest count density and the percent of diffuse perfusion in each region was determined. A (highest) − B (another region) × 100/A = percent diffuse perfusion. Deficits greater than 25 percent diffuse perfusion, if present in one or more regions in two or more views, were considered abnormal.

Interpretation of resting and exercise electrocardiograms: Resting and exercise electrocardiograms were interpreted by two independent observers without knowledge of the clinical diagnosis or angiographic findings. Seven patients whose resting electrocardiograms demonstrated voltage criteria for left ventricular hypertrophy with ST-T wave abnormalities were considered to have uninterpretable exercise electrocardiograms because of the known high incidence rate of false-positive tests in these patients. Exercise electrocardiograms in the remaining three patients were considered positive for ischemia if horizontal or downsloping S-T segment depression equal to or greater than 1 mm 0.08 second after the J point developed in the monitoring leads during exercise or in the postexercise tracings.

TABLE II

Results of Electrocardiogram, Treadmill Exercise Test and Thallium-201 Scan

Case no.	Resting Electrocardiogram	S-T Depression on Stress Test	Achieved Heart Rate (% max.)	Reason for Stopping	Exercise Perfusion Scintigram
1	NSR, LVH	2 mm	85	Target rate achieved	Normal
2	NSR, LVH	1 mm	71	Chest pain; S-T depression	Normal
3	NSR, LVH	1 mm	60	Chest pain; S-T depression	Normal
4	NSR, LVH	2 mm	65	Chest pain; S-T depression	Normal
5	NSR, normal	2 mm	85	Target rate achieved	Normal
6	NSR, LVH	2 mm	60	Chest pain; S-T depression	Abnormal
7	NSR, normal	Normal	85	Target rate achieved	Normal
8	NSR, LVH	1 mm	54	Chest pain; S-T depression	Normal
9	NSR, LVH	1.5 mm	85	Target rate achieved	Normal
10	NSR, normal	Normal	85	Target rate achieved	Normal

LVH = left ventricular hypertrophy; max. = maximal; NSR = normal sinus rhythm.

Results

Table II lists the results of electrocardiography, stress tests and perfusion scintigraphy in each patient. All patients had normal coronary anatomy documented angiographically.

Resting electrocardiograms: All patients had normal sinus rhythm. Seven of 10 patients had evidence of left ventricular hypertrophy with accompanying S-T segment depressions or T wave inversions, or both, in the resting electrocardiogram. Three patients had a normal resting electrocardiogram.

Exercise tests: In the seven patients with an abnormal resting electrocardiogram due to the presence of left ventricular hypertrophy, treadmill testing resulted in further increases in S-T segment depressions of at least 1 mm during exercise or in the postexercise period. In five of the seven patients, substernal chest pain developed necessitating termination of exercise.

Of the three patients with a normal resting electrocardiogram, two had normal results on the exercise stress test. The remaining patient had markedly abnormal results on the treadmill test with 2 mm horizontal S-T segment depressions in leads II, III, aVF and V_3 to V_5. No patient had chest pain during exercise testing.

Myocardial perfusion scintigrams: Nine of 10 patients had normal stress perfusion scintigrams as judged by both unenhanced analog images and computer-enhanced images. Of particular interest was Patient 5, a 45 year old white man, who had previously undergone two cardiac catheterizations because of persistent, severe exertional chest pain. Coronary angiography gave normal results on both occasions, and the presence of idiopathic hypertrophic subaortic stenosis was not diagnosed. Figures 1 and 2 display the stress electrocardiogram and scintigrams of this patient. The resting electrocardiogram was normal; however, stress electrocardiograms revealed significant S-T segment depressions in leads II, III, aVF and V_3 to V_5. Myocardial perfusion imaging was normal. Echocardiography revealed the presence of systolic anterior motion of the anterior leaflet of the mitral valve with septal hypertrophy.

One patient had a normal resting myocardial perfusion scintigram but a markedly abnormal stress scan with diminished thallium-201 uptake in the anterior, anteroseptal and anterolateral portions of the left ventricle (Fig. 3).

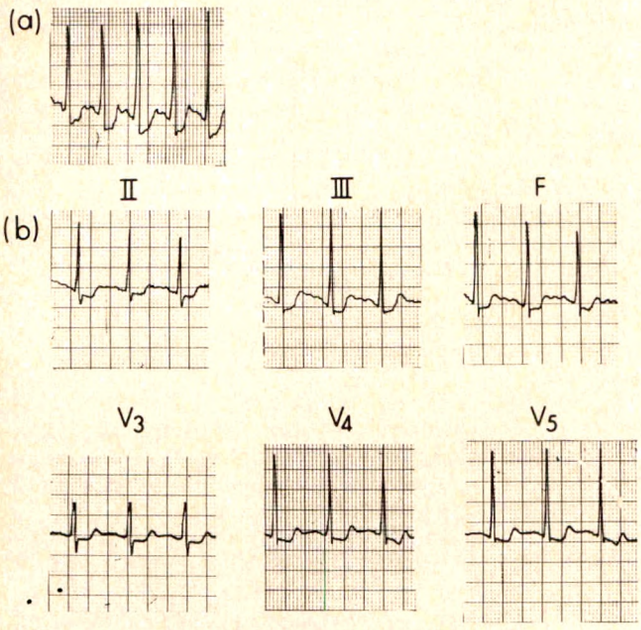

FIGURE 1. Patient 5 with a normal resting electrocardiogram. **a**, exercise monitoring lead V_5 demonstrating 3-mm S-T segment depression. **b**, 2 minute postexercise electrocardiogram demonstrating horizontal and downsloping S-T segments in limb and precordial leads. F = lead aVF.

Discussion

The occurrence of chest pain, with or without associated coronary artery disease, in patients with idiopathic hypertrophic subaortic stenosis is well recognized. Clinical evaluation combined with echocardiography has proved to be highly reliable in establishing the diagnosis of idiopathic hypertrophic subaortic stenosis[4,5]; however, the evaluation of anginal chest pain in these patients has continued to present a diagnostic problem. Abnormalities of the resting electrocardiogram, including abnormal Q waves in the inferior and

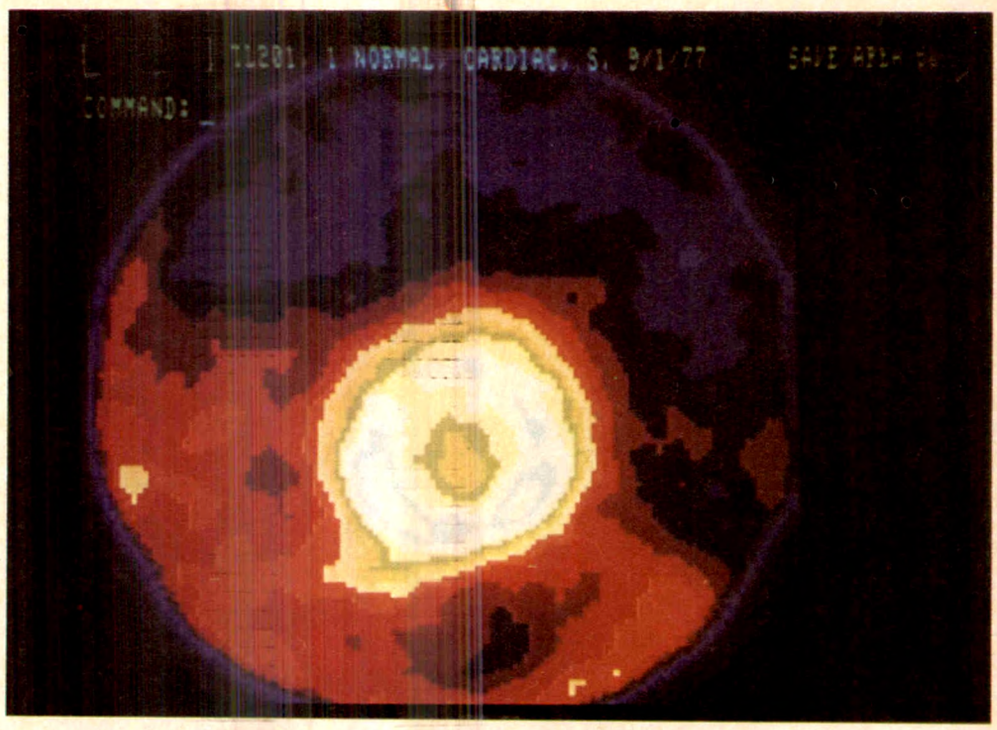

FIGURE 2. Patient 5. Exercise myocardial perfusion scan in 45° left anterior oblique projection showing homogeneous uptake of thallium-201 by the left ventricle. The image was computer processed, with each step in the color wheel representing approximately a 6.5 percent change in counts. White represents the greatest activity, purple the lowest.

lateral precordial leads, as well as left ventricular hypertrophy with ST-T wave abnormalities, further contribute to the difficulties in diagnosis.

The role of exercise testing in hypertrophic cardiomyopathy: The ability of exercise testing to establish the diagnosis of coronary artery disease in patients with idiopathic hypertrophic subaortic stenosis has not previously been evaluated. In general, overall results of treadmill stress testing have been variable depending on the criteria employed, the method of exercise and the extent of coronary disease.[12–15]

Although treadmill exercise testing aids in the diagnosis of coronary artery disease, electrocardiographic evidence of left ventricular hypertrophy has been as-

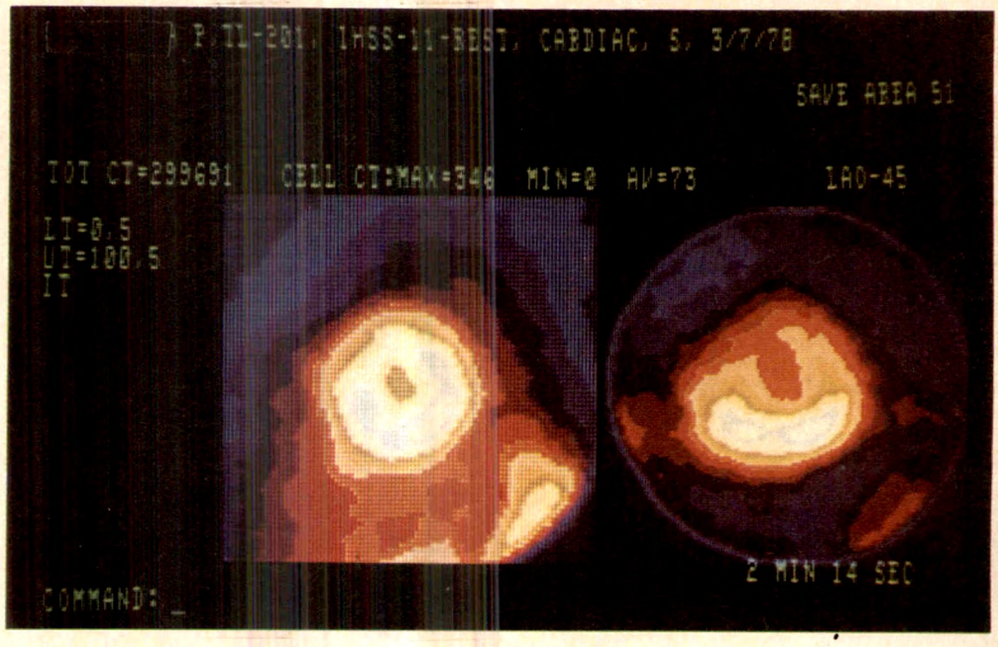

FIGURE 3. Patient 6. Resting and exercise scans in the 45° left anterior oblique position taken 10 days apart. The resting scan (**left**) shows homogeneous uptake of thallium-201 in the shape of a closed doughnut; the exercise scan (**right**) shows relative hypoperfusion of the anteroseptal and anterolateral portions of the left ventricle suggesting ischemia in the distribution of the left anterior descending coronary artery. The color changes in the hypoperfused area reflect a 40 percent decrease in counts compared with counts in the normally perfused areas.

sociated with wide variability in treadmill response, rendering the test uninterpretable. Harris et al.[8] performed treadmill exercise tests in 16 patients with left ventricular hypertrophy. In 14 patients, worsening S-T segment depressions were noted whereas in 2 patients there were no changes in the S-T segments. In both groups, 50 percent of patients had coronary artery disease whereas the other 50 percent had normal coronary arteries. In our patients with idiopathic hypertrophic subaortic stenosis, all seven patients with electrocardiographic evidence of left ventricular hypertrophy had worsening S-T segment depressions during exercise whereas one of three with a normal resting electrocardiogram had an abnormal treadmill response. Because every patient had normal coronary arteries, stress testing was not helpful in identifying those patients with normal arteries.

Role of myocardial perfusion imaging versus electrocardiographic exercise testing: The development of techniques for myocardial perfusion imaging has provided a useful, noninvasive method for assessing relative myocardial hypoperfusion.[16–19] Although the sensitivity of myocardial perfusion imaging varies with the number and location of vessels involved, several studies suggest it is more sensitive than treadmill exercise testing alone.[17–19] When abnormalities in both exercise electrocardiograms and myocardial perfusion images are present, the sensitivity and specificity approach 90 percent.[18,19] Thus, stress myocardial perfusion imaging might play an extremely important role in ferreting out true false-positive stress test results as well as aid in the interpretation of test results in patients with preexisting electrocardiographic abnormalities.[19–21]

In our study, 9 of 10 patients with idiopathic hypertrophic subaortic stenosis and normal coronary arteries had normal exercise scintigrams. Patient 6, a 48 year old woman, had a markedly abnormal exercise scan despite a completely normal resting scan. The scan indicated ischemia of the anterior and anterolateral walls and septum. Angiograph (Fig. 4) revealed unusually massive hypertrophy of the anterior wall of the left ventricle, suggesting that the balance between left ventricular mass and coronary blood supply was much more critical in this patient than in the remaining nine.

All seven patients with electrocardiographic evidence of left ventricular hypertrophy demonstrated further S-T segment depressions of at least 1 mm during exercise, and in five patients typical anginal chest pain developed during the exercise period. Nevertheless, six of the seven patients had normal exercise perfusion scintigrams, suggesting the superiority of this technique over electrocardiopathic exercise testing or clinical evaluation in assessing the coronary status in the presence of idiopathic hypertrophic subaortic stenosis.

Mechanisms of angina in hypertrophic cardiomyopathy: Chest pain associated with idiopathic hypertrophic subaortic stenosis is quite common,[22–26] but its mechanisms are not well understood. It is important to exclude coexisting coronary artery disease in patients in the age group prone to this disease[1–3] because it might be the cause of chest pain. A recent study has suggested that septal perforator arterial compression was a cause of chest pain in some patients with idiopathic hypertrophic subaortic stenosis,[25] but this phenomenon was not observed in any of our patients. Because a significant number of our patients (60 percent) had exertional chest pain, diminished myocardial blood flow might indeed be responsible for causing chest pain in these patients. That relative myocardial perfusion scanning failed to reveal abnormalities in 9 of 10 patients studied suggests that the pain might be secondary to diffusely or homogeneously diminished perfusion or to unrecognized metabolic abnormalities. The occurrence of an abnormal exercise perfusion scintigram in Patient 6 indicates that relative myocardial perfusion abnormalities in the absence of coronary artery disease might occasionally be seen. Ventriculography in this patient revealed rather massive hypertrophy of the anterior left ventricular wall that may have given rise to a marked disproportion in blood flow/unit mass (Fig. 4). Although Weiss et al.[26] studied myocardial blood flow in hypertrophic cardiomyopathy using radioactive xenon 133 and observed diffuse depression of myocardial perfusion (blood flow/unit mass) throughout the left ventricle, it is possible that relative perfusion abnormalities can occur in areas of marked ventricular hypertrophy. Bulkley et al.[27] reported normal myocardial perfusion scans in seven of eight patients with idiopathic congestive cardiomyopathy. In this group of patients, four had a history of chest pain and two had a history of possible myocardial infarction. Finally, increased lactate production has been observed in patients with chest pain and normal coronary arteries, suggesting the

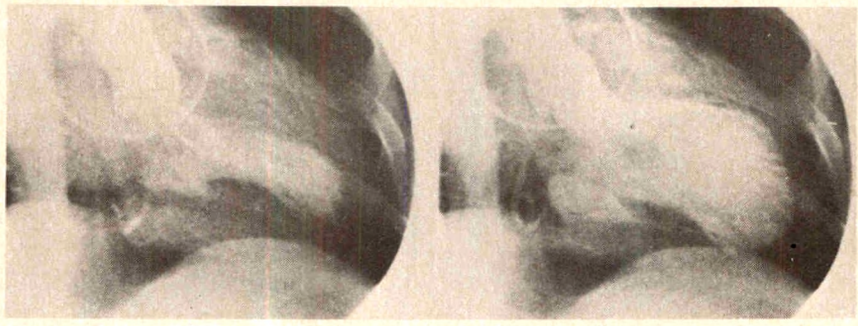

FIGURE 4. Patient 6. Left ventriculography in the 30° right anterior oblique projection in end-diastole (**right**) and end-systole (**left**). With the left anterior descending artery as an epicardial marker, note the enormous hypertrophy in the region of the left ventricular outflow tract and the proximal half of the anterior wall.

presence of metabolic derangements with tissue hypoxia in the absence of major coronary artery disease.[28] None of our patients were studied to evaluate this possibility.

Clinical implications: Since the initiation of our investigation, we have not had the opportunity to study patients with coexisting idiopathic hypertrophic subaortic stenosis and coronary artery disease. However, the use of myocardial perfusion imaging in the detection of exercise-induced myocardial ischemia in coronary artery disease has been well documented[9–11,16–21] and our own experience parallels the published data. We would expect that the results in patients having both idiopathic hypertrophic subaortic stenosis and coronary artery disease would be comparable. The presence of asymmetric septal thickening in itself did not produce abnormal scans.

Although the cause of chest pain in patients with idiopathic hypertrophic subaortic stenosis and normal coronary anatomy continues to be obscure, relative myocardial perfusion scintigraphy with thallium-201 appears to be a useful noninvasive technique that assists in ruling out significant coronary artery disease in these patients.

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Left Bundle Branch Block: Angiographic Segmental Wall Motion Abnormalities

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Ventricular wall motion as studied with contrast ventriculography has been judged normal in the few previously reported cases of patients with left bundle branch block who have neither coronary artery disease nor diffuse cardiomyopathy. However, recent echocardiographic studies have demonstrated a high frequency of segmental asynergy of the septal wall in such patients. In this study left ventricular wall motion was analyzed in 15 patients with left bundle branch block and without significant coronary artery disease or diffuse cardiomyopathy. Biplane cineangiograms from these patients were compared with those from 100 consecutive patients with normal intraventricular conduction and without coronary artery disease or cardiomyopathy using two techniques: qualitative visual inspection and a computer-assisted quantitative method.

By qualitative review, 6 of 15 patients with left bundle branch block had regional akinesia or dyskinesia as compared with none of 100 patients with normal intraventricular conduction (chi square = 42.3; $P < 0.001$). By quantitative review, 10 of 12 patients with left bundle branch block had abnormal wall motion along at least one hemiaxis. It is concluded that angiographic regional wall motion abnormalities are common in patients with left bundle branch block, even in the absence of coronary artery disease or diffuse cardiomyopathy. The abnormalities may result from the abnormal sequence of ventricular activation rather than from myocardial fibrosis.

Segmental asynergy of the left ventricle as demonstrated by contrast ventriculography correlates strongly at postmortem examination with myocardial fibrosis due to prior myocardial infarction.[1] Patients with left bundle branch block and clinically manifest coronary artery disease commonly demonstrate segmental asynergy.[2] However, asynergy of the interventricular septum has been demonstrated with echocardiography in patients with left bundle branch block in the absence of coronary artery disease.[3,4] The purpose of our study was to assess with left ventricular cineangiography the frequency and severity of segmental wall motion abnormalities in patients with left bundle branch block and no coronary artery disease.

Because myocardial infarction is rare in patients without coronary artery disease,[5,6] we hypothesized that segmental asynergy in patients without coronary artery disease could be caused by an abnormal sequence of ventricular activation rather than by myocaridal fibrosis.

Methods

Patients: Seventeen patients with complete left bundle branch block who underwent cardiac catheterization in the Duke cardiovascular laboratory between 1971 and 1978 met the following criteria: (1) no narrowing of any major coronary artery exceeding 25 percent of the vessel diameter determined with selective coronary angiography in multiple views; (2) no previous documented myocardial infarction; and (3) no diffuse, as opposed to segmental, wall motion abnormalities.

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Fifteen patients had technically adequate contrast ventriculograms available for review (3 single plane and 12 biplane). Among these, there were seven men and eight women who ranged in age from 27 to 69 years (median 49). All of the patients underwent cardiac catheterization to aid in the diagnosis of chest pain, although only 2 of the 15 patients were classified by an examining cardiologist at the time of catheterization as having typical angina pectoris. One patient had aortic and mitral insufficiency with cardiomegaly and symptoms of congestive heart failure in addition to chest discomfort, but no other patient had congestive failure or cardiomegaly. One other patient had mitral valve prolapse without mitral insufficiency, but no other patient had valvular heart disease of any form. Four patients demonstrated a fourth heart sound gallop but in no patient was a third heart sound gallop detected. Six patients had a history of hypertension. Left ventricular end-diastolic pressures at catheterization ranged from 4 to 16 mm Hg (median 9).

The study group was compared with 100 control patients meeting the same criteria in the absence of left bundle branch block.

Qualitative ventriculographic data: The contrast left ventriculograms of the 15 patients with left bundle branch block and 100 patients without left bundle branch block were viewed without knowledge of the electrocardiographic findings. The right anterior oblique projection was used to assess the anterior, apical and inferior walls of the left ventricle; the left anterior oblique view was used to assess the lateral and septal walls. The contraction of each wall was classified as normal, asyneretic, akinetic, or dyskinetic. Asyneresis was defined as decreased systolic wall motion, akinesia as absent systolic wall motion and dyskinesia as paradoxic or outward bulging of the ventricular wall during systole. Because the subjective observation of asyneresis is frequently equivocal, we limited our analysis to severe wall motion abnormalities, that is, akinesia or dyskinesia.

Quantitative ventriculographic data: Twelve of the study patients with left bundle branch block had technically adequate biplane ventriculograms for computer-assisted digitization as previously reported from this laboratory.[1] The left ventricular silhouette in these patients was traced at end-diastole and end-systole on a rear projection screen fitted with a sonic digitizer interfaced with a PDP-11/45 computer. The beat selected for analysis was remote from premature ventricular contractions and within the first five opacified beats to avoid the deleterious effects of contrast medium.[7] The quantitative wall motion analysis was determined from these digitized ventricular silhouettes. A longitudinal axis connecting the middle of the aortic valve and the apex was constructed for both the end-diastolic and end-systolic images. The longitudinal axis was divided into five segments of equal length, and hemiaxes perpendicular to the longitudinal axis were constructed to the edge of the silhouette. The apical hemiaxis was represented by the fraction of the longitudinal axis extending from the apex to the point of crossing of the two adjacent horizontal hemiaxes.

The percent shortening of each hemiaxis was determined by the formula: Percent shortening = diastolic length − systolic length/diastolic length × 100. The normal values for percent hemiaxis shortening were determined in 58 normal patients, and quantitatively determined asynergy was defined as decreased shortening greater than 2 standard deviations from the normal mean.[1] Because of large standard deviations in systolic shortening of the two hemiaxes adjacent to the aortic valve, these segments were not considered in our study. The quantitative ventriculographic data from a normal subject illustrating these methods are given in Figure 1.

Results

Qualitative wall motion analysis: We observed severe abnormalities of segmental wall motion in 6 of the 15 patients with left bundle branch block and in none of the 100 patients without left bundle branch block (chi square = 42.3; $P < 0.001$). Severe segmental asynergy of the septum was present in four patients: akinesia in one and dyskinesia in three. Severe asynergy also was observed in the anterior or apical walls of three patients. Figure 2 depicts the right anterior oblique view at end-diastole and end-systole of a contraction sequence observed in one of our patients with left bundle branch block and demonstrates dyskinesia of the anterior wall.

Quantitative wall motion analysis: An earlier study[8] in this laboratory using the quantitative wall motion program in 30 unselected normal patients showed that the percent shortening of all hemiaxes was within 2 standard deviations of the normal values derived from our initial control series of 58 normal patients.[1] Consequently, the data from the 100 normal control subjects in this series were not analyzed quantitatively. Among our 12 patients with left bundle branch block studied with the quantitative technique, 10 had abnormal systolic shortening along at least one of the seven hemiaxes considered in this study in either the right or the left anterior oblique projection. Five patients had abnormalities of anterior, apical or inferior wall motion identified in the right anterior oblique projection; four patients had abnormalities of septal or lateral wall motion as seen in the left anterior oblique projection; and one patient had abnormalities involving the apical and inferior walls visualized in both views.

Figure 3 demonstrates the quantitative ventriculographic analysis of the same patient whose cineangiographic frames are shown in Figure 2. In this patient, quantitative analysis also documented ventricular asynergy involving the anterior wall in the right anterior oblique view. Although in this patient the abnormalities demonstrated with the qualitative and quantitative techniques were comparable, the methods did not yield identical interpretation in all patients. The qualitative method showed abnormalities in 40 percent of the patients studied whereas the quantitative method demonstrated abnormalities in 83 percent. Because the

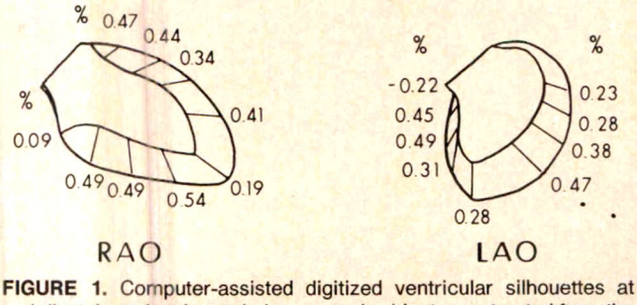

FIGURE 1. Computer-assisted digitized ventricular silhouettes at end-diastole and end-systole in a normal subject, constructed from the right anterior oblique (RAO) and left anterior oblique (LAO) projections. The numbers represent the percent systolic shortening along each of nine hemiaxes in each projection, calculated as stated in the text.

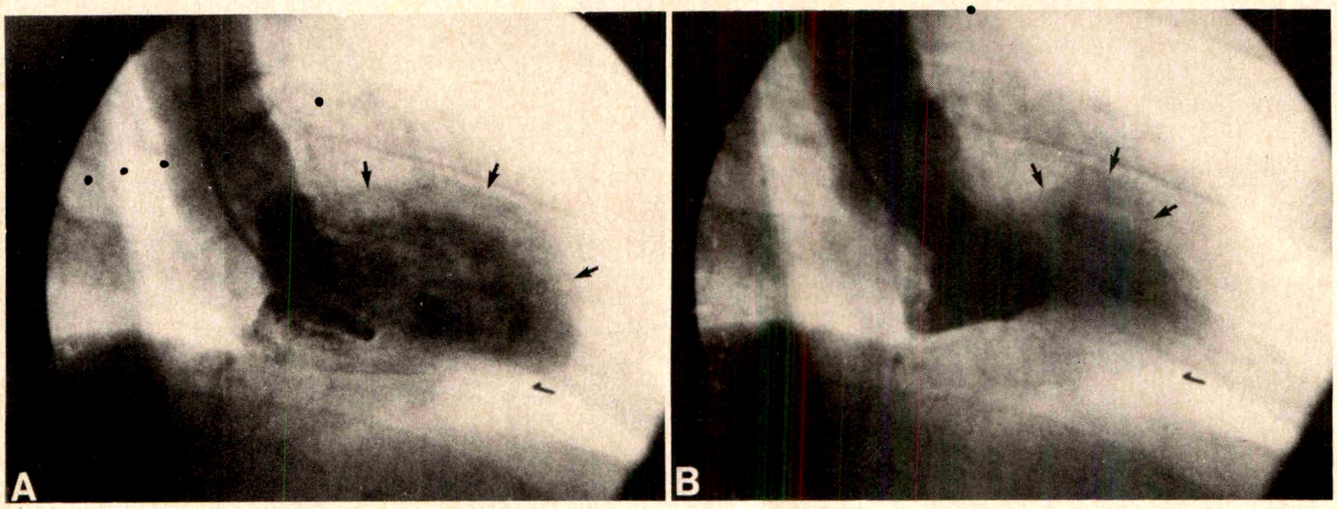

FIGURE 2. Single frame photographs of the cardiac silhouette during contrast ventriculography in the right anterior oblique projection at end-diastole (**A**) and end-systole (**B**) in a patient with left bundle branch block without coronary artery disease. Note the dyskinetic anterior wall (**arrows**).

methods are not strictly comparable, this apparent discrepancy was not unexpected. The qualitative method allows visual integration of the entire contraction sequence, thereby revealing transient abnormalities as well as those that are evident at end-systole. The quantitative method only compares a single end-systolic silhouette of the ventricle with a single end-diastolic silhouette. Although we limited the qualitative assessment to severe abnormalities of segmental wall motion. (akinesia and dyskinesia), the quantitative approach was not similarly limited and may have identified milder abnormalities.

A frame by frame analysis of wall motion in the patients noted to have the most severe regional wall motion abnormalities was performed. In patients with septal wall asynergy we observed that normal posterior motion of the septum was viewed in the left anterior oblique projection during the initial 50 to 100 msec of systole followed by subsequent abnormal anterior motion of the septum in later systole. Although the methods are not strictly comparable, this sequence corresponds roughly to the echocardiographic findings reported in patients with left bundle branch block.[3,4] The difficulty in aligning the camera angle parallel to the true septum during angiography may explain why we observed a lesser prevalence of septal wall motion abnormalities than that found with echocardiography in similar patients. We observed no consistent sequential pattern for the wall motion abnormalities seen in other regions of the heart.

Clinical follow-up study: The clinical course of these patients with a follow-up interval ranging from 6 months to 5 years (median 3.5 years) indicates an excellent prognosis with no deaths. This contrasts sharply with our experience in patients with left bundle branch block and coronary artery disease who have a poor prognosis.[2]

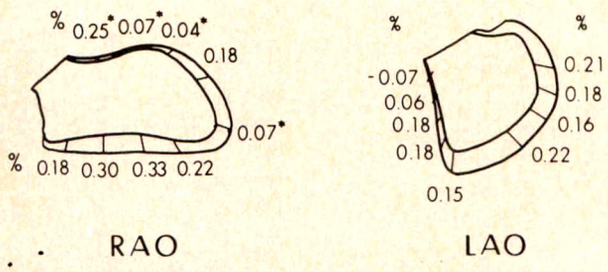

FIGURE 3. Same patient. Computer-assisted digitized ventricular silhouettes at end-diastole and end-systole in the patient with left bundle branch block whose cineangiographic frames are depicted in Figure 2. The numbers represent the percent systolic shorting along each hexiaxis as described in the length to Figure 1 and in the text. **Asterisks** denote values deviating more than 2 standard deviations from the mean observed in 58 normal subjects.

Discussion

Our data, derived by two different forms of analysis, demonstrate that segmental wall motion abnormalities observed on contrast left ventriculography are common in patients with left bundle branch block in the absence of coronary artery disease or diffuse cardiomyopathy. These observations differ from those of prior reports[9,10] of normal ventricular contraction patterns during contrast ventriculography in patients with left bundle branch block without coronary artery disease, but they support echocardiographic data citing frequent septal wall asynergy in such patients.[3,4]

Etiology of wall motion abnormalities: Without histologic data, we can only speculate as to the etiologic basis of the segmental asynergy observed in these patients. These findings may be related to an altered sequence of ventricular activation associated with left bundle branch block but without abnormalities of the ventricular myocardium itself. If so, the features of the activation sequence inducing the asynergy must be present in some patients with left bundle branch block but not in others, because all patients do not demonstrate asynergy.

Myocardial infarction without coronary artery disease is rare,[5,6] making it unlikely that fibrosis from prior myocardial infarction caused the segmental asynergy we observed. Patients like ours with left bundle branch block seem to represent a subgroup in which the previously observed high correlation between segmental asynergy and myocardial infarction is absent.

We cannot exclude the possibility that segmental myocardial fibrosis caused by factors other than prior myocardial infarction exists in these patients. However, none of our patients had diffuse asynergy indicative of cardiomyopathy, and none had systemic manifestations of disease states such as sarcoidosis or hemochromatosis which may be associated with an infiltrative cardiomyopathy. Valve disease or rheumatic myocardial involvement may have played a role in the segmental asynergy observed in our patient with aortic and mitral insufficiency, although chronic volume overload usually leads to diffuse rather than segmental dysfunction. Likewise, mitral valve prolapse may have led to the asynergy observed by computer analysis of end-systolic and end-diastolic cineangiographic frames in our patient with this disorder,[11] but this patient showed only mild asyneresis on qualitative visual review of the ventriculogram and was thus classified as normal. Even if these two patients had been excluded, we still observed an unexpectedly high prevalence of segmental wall motion abnormalities, indicating that valvular heart disease could not be the only factor producing ventricular asynergy in patients with normal coronary arteries and left bundle branch block.

Implications: Segmental wall motion abnormalities are common in patients with left bundle branch block in the absence of coronary artery disease. Therefore, such abnormalities should not be considered diagnostic of prior myocardial infarction or regional ischemia in these patients. The prognosis for patients with left bundle branch block without coronary artery disease or cardiomyopathy is good: There were no deaths in our group at a mean follow-up time of 3.5 years. We can only speculate that the segmental asynergy seen in these patients is more likely related to an abnormal sequence of left ventricular activation than to segmental myocardial fibrosis.

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Performance of the Failing and Nonfailing Right Ventricle of Patients With Pulmonary Hypertension

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Hemodynamic performance of the right ventricle was measured in 34 patients: 17 with pulmonary hypertension, 9 with pulmonary hypertension and right ventricular failure and 8 control subjects. Among the patients with pulmonary hypertension who did not have right ventricular failure, right ventricular maximal isovolumic rate of development of ventricular pressure (dP/dt) was significantly elevated ($P < 0.001$), whereas maximal 1/P dP/dt and maximal velocity of contractile element shortening (V_{max}) were comparable with values observed in control subjects. The patients with pulmonary hypertension who had right ventricular failure also showed an augmented right ventricular maximal dP/dt ($P < 0.001$) and normal 1/P dP/dt and V_{max}. These observations indicate that in pulmonary hypertensive heart disease, even when the right ventricle failed in a clinical sense, the contractile effort was normal. Consequently, right ventricular failure may develop in patients with pulmonary hypertensive heart disease even though the cardiac muscle performs normally as a contractile tissue.

Pulmonary hypertensive heart disease is the late manifestation of primary pulmonary hypertension, pulmonary valve stenosis, pulmonary embolism and pulmonary hypertension secondary to mitral stenosis or left ventricular failure.[1] The definition of pulmonary hypertensive heart disease excludes patients with "emphysema heart" because polycythemia and hypoxia may have additional deleterious effects upon the heart.[1] Although the central hemodynamics in pulmonary hypertensive heart disease have been extensively described, little is known about the contractile state of the right ventricle in such patients.

The purpose of this paper is to describe the contractile behavior of the failing and nonfailing right ventricle in pulmonary hypertensive heart disease. Indexes that are commonly used to assess left ventricular contractile performance were measured in the right ventricle of patients with normal pulmonary arterial pressure, in patients with pulmonary hypertension and in patients with pulmonary hypertension and right ventricular failure. An evaluation of right ventricular contractile performance in pulmonary hypertensive heart disease, both in patients in a compensated state and in those with right ventricular failure, may contribute to the understanding of this disease entity.

Methods

Patients: Contractile performance of the right ventricle was evaluated in 34 patients who underwent diagnostic cardiac catheterization. Eight had normal pulmonary arterial pressure, 17 had pulmonary hypertension without right ventricular failure and 9 had pulmonary hypertension with right ventricular failure.

Patients were categorized as having a normal pulmonary arterial pressure if it did not exceed 30/12 mm Hg.[2] Because right ventricular dysfunction has been observed in patients with right coronary disease,[3,4] such patients were

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excluded from the control group if narrowing of the right coronary artery was present.

Right ventricular failure was defined as the presence of hepatomegaly, ascites or dependent edema in patients with an elevated (greater than 9 mm Hg) right atrial pressure.[2] Thus, the diagnosis of right ventricular failure was essentially a clinical diagnosis,[5–7] although measured pressures were substituted for the physical sign of systemic venous hypertension.

Patients were excluded if they had tricuspid regurgitation or an intracardiac shunt. They were also excluded if they had chronic obstructive pulmonary disease because "emphysema heart" may differ from pulmonary hypertensive heart disease.[1] The hemoglobin of control subjects, patients with pulmonary hypertension and patients with pulmonary hypertension and right ventricular failure was, respectively, 14.5 ± 0.8, 13.5 ± 0.5, and 13.5 ± 0.7 g/100 ml (mean ± standard error of the mean). The systemic arterial oxygen saturation of patients with pulmonary hypertension was 96 ± 1 percent and in those with pulmonary hypertension and right ventricular failure it was 96 ± 2 percent.

Clinical features of patients: The cardiac diagnoses of the patients in this study are shown in Table I. Patients with pulmonary hypertension (54 ± 3 years) and those with pulmonary hypertension and right ventricular failure (55 ± 3 years) were older than the control subjects (41 ± 4 years). None of the control subjects were treated with digitalis or propranolol. Twelve of the 17 patients with pulmonary hypertension who did not have right ventricular failure and all 9 patients with right ventricular failure were treated with digitalis. No significant difference in any of the measured hemodynamic variables was observed between the patients with pulmonary hypertension who were treated with digitalis and those who were not. Therefore, the data are reported together.

No patient had electrocardiographic evidence of right ventricular hypertrophy. P pulmonale was present in one patient with pulmonary hypertension who did not have right ventricular failure. Complete right bundle branch block was present in one and right axis deviation in another patient with right ventricular failure. The criteria we selected for making electrocardiographic interpretations have previously been described.[8]

Hemodynamic measurements: All pressures were measured with Millar (Houston) catheter-tip micromanometers. Indexes of contractile performance, including the maximal isovolumic rate of development of ventricular pressure (dP/dt), maximal 1/P dP/dt and maximal velocity of contractile element shortening (V_{max}) were calculated with the aid of a computer as previously described.[9] V_{max} and maximal 1/P dP/dt were calculated on the basis of the actual pressure.[10,11] Right ventricular work was calculated as the product of cardiac index and the difference between right ventricular systolic mean pressure and right ventricular end-diastolic pressure.[2,12]

TABLE I

Cardiac Diagnoses

Control subjects	
No heart disease	6
Coronary heart disease (left anterior descending artery only)	1
Aortic insufficiency, mild	1
Total	8
Pulmonary hypertension	
Coronary heart disease	5
Mitral stenosis or regurgitation, or both	7
Aortic stenosis and regurgitation	1
Cardiomyopathy	2
Cause undetermined	2
Total	17
Pulmonary hypertension with right ventricular failure	
Coronary heart disease	5
Aortic stenosis	1
Cardiomyopathy	2
Mitral stenosis and regurgitation	1
Total	9

Results

Central hemodynamic measurements (Table II): In comparison with control subjects, patients with pulmonary hypertension not accompanied by right ventricular failure had a lower cardiac index (2.1 ± 0.2 versus 2.9 ± 0.2 liters/min per m^2) ($P < 0.02$) and a lower stroke index (24 ± 2 versus 38 ± 3 ml/beat per m^2) ($P < 0.01$). The pulmonary vascular resistance was higher than in control subjects (310 ± 60 versus 50 ± 10 dynes sec cm^{-5}) ($P < 0.02$), as was the work per minute performed by the right ventricle (0.94 ± 0.12 versus 0.40 ± 0.07 kg-m/min per m^2) ($P < 0.02$) and the right ventricular end-diastolic pressure (6 ± 1 versus 2 ± 1 mm Hg) ($P < 0.01$).

The pulmonary arterial pressure of patients with pulmonary hypertension and failure (70/38 ± 5/2 mm Hg) was higher than in patients without failure ($P < 0.01$) as was pulmonary vascular resistance (510 ± 40 dynes sec cm^{-5}) ($P < 0.05$) (Table II). Right ventricular end-diastolic pressure (13 ± 1 mm Hg) was also higher ($P < 0.001$) and cardiac index (1.5 ± 0.04 liters/min per m^2) was lower ($P < 0.05$).

Isovolumic indexes of contractile performance: Patients with pulmonary hypertension had a higher maximal dP/dt than control subjects (500 ± 30 versus 200 ± 20 mm Hg/sec) ($P < 0.001$) (Fig. 1). No significant difference in patients with pulmonary hypertension compared with control subjects was observed in maximal 1/P dP/dt (41 ± 4 versus 31 ± 5 sec^{-1}) and in V_{max} (1.86 ± 0.11 versus 1.55 ± 0.13 sec^{-1}) (Fig. 1).

In patients with right ventricular failure maximal dP/dt was also higher than in control subjects (610 ± 70 versus 200 ± 20 mm Hg/sec) ($P < 0.001$). The 1/P dP/dt and V_{max} in patients with right ventricular failure did not differ significantly from values in control subjects (25 ± 3 versus 31 ± 5 sec^{-1} and 1.42 ± 0.14 versus 1.55 ± 0.13 sec^{-1}, respectively) (Fig. 1). Maximal 1/P dP/dt and V_{max} in patients with right ventricular failure were lower than in patients with pulmonary hypertension who did not have failure ($P < 0.01$ and $P < 0.02$, respectively); no significant difference was observed in maximal dP/dt.

Right ventricular maximal dP/dt correlated with both pulmonary arterial systolic and diastolic pressures ($r = 0.77$ and $r = 0.81$, respectively) (Fig. 2). The correlations were somewhat better if patients with failure were excluded ($r = 0.84$ and $r = 0.89$, respectively). Maximal

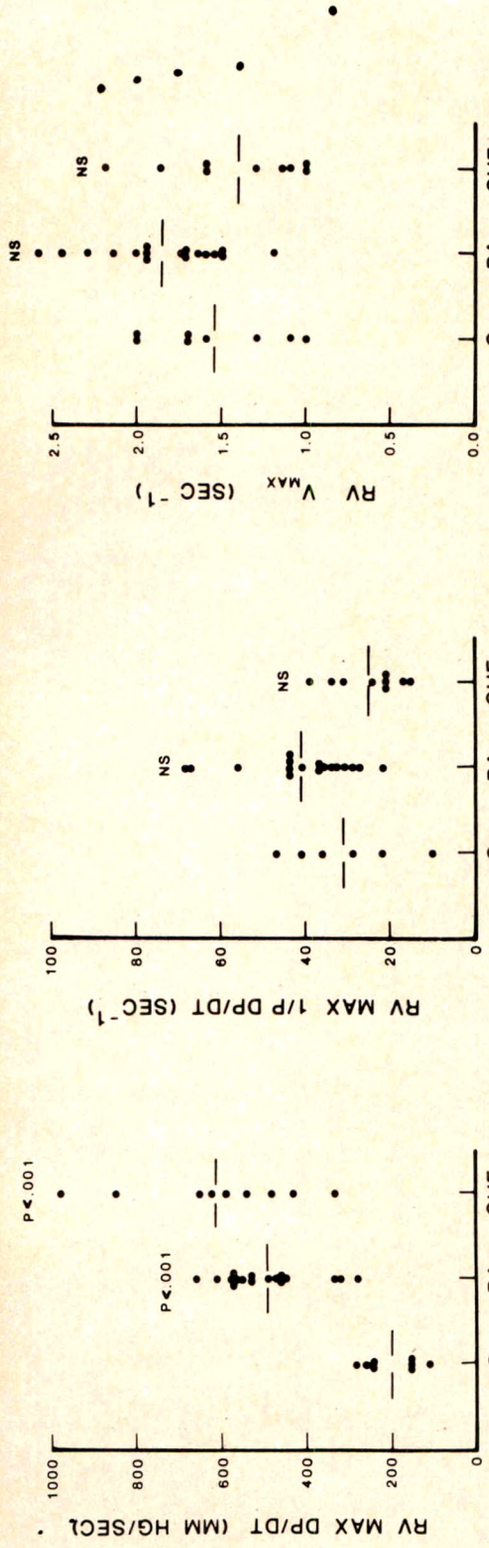

FIGURE 1. Right ventricular (RV) contractile performance in control subjects (C), patients with pulmonary hypertension (PA HTN) and patients with pulmonary hypertension and right ventricular failure (CHF). Maximal right ventricular rate of change of pressure (MAX dP/DT) (**left**), maximal 1/P DP/DT (**center**) and maximal velocity of contractile element shortening (V_{MAX}) (**right**) are shown. All probabilities refer to comparisons of patients with pulmonary hypertension with control subjects or comparisons of patients with right ventricular failure with control subjects.

right ventricular dP/dt showed an approximate correlation with right ventricular end-diastolic pressure (r = 0.67) (Fig. 3).

Discussion

Several assumptions are implicit in the application of isovolumic indexes of myocardial contractile performance to the intact ventricle.[13] Many of these assumptions cannot be justified in the left ventricle,[13] and the problems of application of these indexes to the right ventricle are comparable. In spite of theoretical and practical problems in applying indexes of contractile performance to the intact heart, some usefulness of various indexes has been established.

Contractile performance of right ventricle in pulmonary hypertension: Our observations suggest that in the presence of pulmonary hypertension and right ventricular failure, the venous pressure may increase to levels that exceed the plasma oncotic level, thereby causing the signs of right ventricular failure. Simultaneously, however, the myocardium may remain normal and ventricular performance, presumably because of the increased preload, may be augmented. Maximal dP/dt, even in patients who had right ventricular failure in association with the pulmonary hypertension, was higher than in control subjects. Maximal 1/P dP/dt and V_{max} in the patients with right ventricular failure were comparable with the values in control subjects.

It has been thought that V_{max} and 1/P dP/dt do not greatly change with preload,[10,11] whereas dP/dt is affected.[14] Yet, if the inotropic state of muscle is equated with the degree of activation of the contractile system, the muscle length influences the inotropic state.[15] In this context, a change of muscle length can be regarded as an inotropic intervention.[15] It appears that even in right ventricular failure, the increased preload produces a stimulus sufficient to cause a high rate of development of pressure that reflects the increased contractile effort necessary to overcome the load imposed upon the right ventricle. The muscle itself, as judged by indexes of contractile performance that are not thought to relate to preload, appears to be unimpaired.

The response of the nonfailing right ventricle to pulmonary hypertension in these patients was similar to the response of the right ventricle to mechanical constriction of the pulmonary artery.[16] After constriction of the pulmonary artery, a steeper isovolumic dP/dt of right ventricular pressure was observed.[16] The response of the failing right ventricle observed in our study was similar to the response noted in dogs in all but the final stages of failure accompanied by shock.[16]

Cardiac output: In spite of the normal isovolumic indexes of contractile performance, cardiac output was low in the patients with pulmonary hypertension and right ventricular failure. The augmented preload appeared to be sufficient to increase the contractile effort but was insufficient to allow the heart to function adequately in the face of the high afterload. Because most of the patients with right ventricular failure had a poorly

TABLE II

Central Hemodynamic Measurements

	Control Subjects (no. = 8)	Pulmonary Hypertension (No CHF) (no. = 17)	Pulmonary Hypertension (CHF) (no. = 9)
PA pressure (mm Hg)			
Mean ± SEM	18/7 ± 1/1	50/25 ± 5/2	70/38 ± 5/2
Range	(13–22/4–12)	(30–86/16–38)	(47–90/25/45)
PA mean pressure (mm Hg)			
Mean ± SEM	10 ± 1	33 ± 4	49 ± 3
Range	(5–15)	(15–54)	(38–60)
RV end-diastolic pressure (mm Hg)			
Mean ± SEM	2 ± 1	6 ± 1	13 ± 1
Range	(1–4)	(2–16)	(5–22)
*P**	. . .	<0.01	<0.001
RA mean pressure (mm Hg)			
Mean ± SEM	4 ± 1	4 ± 1	14 ± 2
Range	(1–7)	(0–8)	(9–20)
*P**	. . .	NS	. . . .
Heart rate (beats/min)			
Mean ± SEM	83 ± 6	87 ± 4	91 ± 4
Range	(60–107)	(60–110)	(72–104)
*P**	. . .	NS	NS
Cardiac index (liters/min per m^2)			
Mean ± SEM	2.9 ± 0.2	2.1 ± 0.2	1.5 ± .1
Range	(2.3–3.3)	(1.4–3.2)	(1.4–1.7)
*P**	. . .	<0.02	<0.001
Stroke index (ml/stroke per m^2)			
Mean ± SEM	38 ± 3	24 ± 2	18 ± 1
Range	(30–49)	(14–48)	(13–24)
*P**	. . .	<0.01	<0.001
PVR (dynes sec cm^{-5})			
Mean ± SEM	50 ± 10	310 ± 60	510 ± 40
Range	(30–80)	(30–830)	(400–700)
*P**	. . .	<0.02	<0.001
RV work (kg-m/min per m^2)			
Mean ± SEM	0.40 ± 0.07	0.94 ± 0.12	0.91 ± 0.05
Range	(0.23–0.65)	(0.38–2.43)	(0.76–1.13)
*P**	. . .	<0.02	<0.001

CHF = congestive heart failure (right-sided); NS = not significant; PA = pulmonary artery; PVR = pulmonary vascular resistance; RA = right atrium; RV = right ventricle; SEM = standard error of the mean.

* Probability (*P*) values refer to comparisons with control subjects.

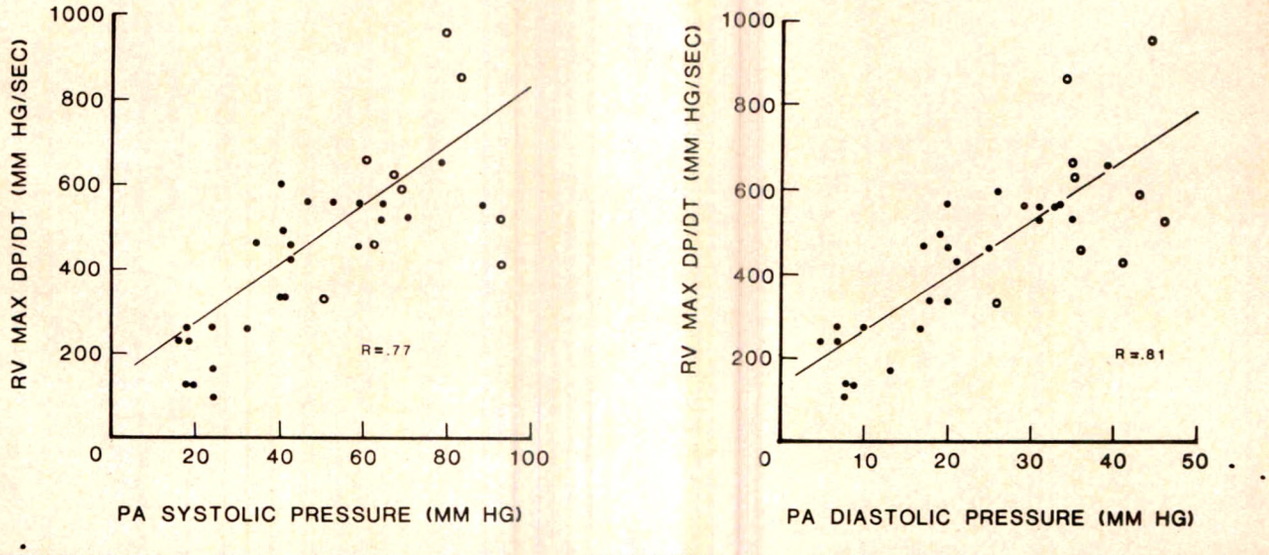

FIGURE 2. Right ventricular (RV) maximal rate of change of pressure (MAX DP/DT) shown as a function of pulmonary arterial (PA) systolic pressure (**left**) and diastolic pressure (**right**). **Open** and **closed circles** represent, respectively, patients with and without right ventricular failure. The regression line and correlation coefficient in each graph relates to all of the patients, irrespective of the presence of right ventricular failure.

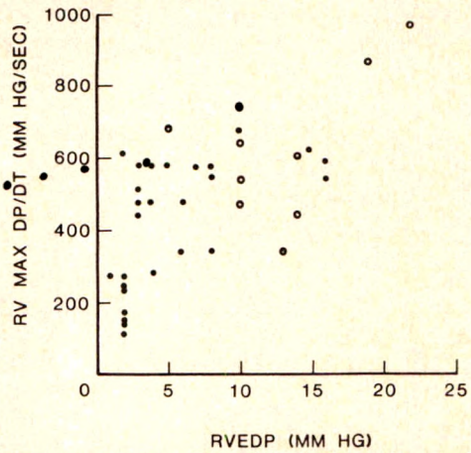

FIGURE 3. Right ventricular (RV) maximal rate of change of pressure (MAX DP/DT) shown as a function of right ventricular end-diastolic pressure (RVEDP). **Open** and **closed circles** represent, respectively, patients with and without right ventricular failure.

contracting left ventricle, the reduced cardiac output may have been partially due to left ventricular dysfunction.[17,18] The latter perhaps could affect right ventricular contractile performance through the interventricular septum which is composed partially of right ventricular muscle,[19] and through muscle bundles that enclose both ventricles.[20]

Right ventricular work and contractile performance: Certainly it is recognized that the work of the right ventricle is increased in pulmonary hypertension. This is described in pulmonary embolism,[21,22] emphysema[23,24] and other forms of pulmonary vascular disease. The increased load imposed on the heart requires an augmented contractile response to maintain the flow at a higher pressure. A "level of hyperfunction" was suggested by experiments in dogs with pulmonary arterial banding,[25] and an augmented right ventricular dP/dt was reported in pulmonary hypertension.[26–28] In our study contractile performance remained normal even in the presence of right ventricular failure. Elevated values of right ventricular dP/dt were observed by others[26,27] in patients with right ventricular failure. Maximal dP/dt, even though it was augmented in comparison with values in normal subjects, was observed by others[26,27] to be low relative to levels predicted on the basis of systolic pressure.

The contractile state of papillary muscle isolated from the hypertrophied and failing right ventricle of cats after banding of the pulmonary artery was depressed.[29] However, the contractile element velocity in the intact right ventricle of such cats was less depressed than in isolated papillary muscle, and right ventricular active wall tension did not differ between animals with congestive heart failure and normal cats.[30] The cats that manifested depressed contractility with failure had significant hypertrophy,[29,30] whereas the electrocardiograms of the patients in our study did not show hypertrophy. Some differences between these studies and our observations in patients may partly relate to the effect of hypertrophy on the contractile performance of the cardiac muscle.[29]

Clinical implications: It may be possible to differentiate failure of a ventricle to perform as a pump from failure of heart muscle to perform as a contractile tissue. It has been speculated[24] that the heart with an excessive pressure load may fail in a clinical sense yet be composed of adequately performing muscles. The patients in our study who had right ventricular failure showed a normal myocardial contractile effort. Therefore, we conclude that right ventricular failure may develop in patients with pulmonary hypertensive heart disease, even though the cardiac muscle performs normally as a contractile tissue.

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Effect of Coronary Arterial Bypass Surgery on Exercise-Induced Ventricular Arrhythmias

Long-Term Follow-Up of a Prospective Randomized Study

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The effect of coronary arterial bypass surgery on exercise-induced ventricular arrhythmias and their relation to sudden death was examined in 102 patients with stable angina pectoris randomly assigned to medical and surgical therapy (54 and 48 patients, respectively). Symptom-limited treadmill tests were performed at entry and at 1 and 5 years. The surgical group demonstrated significant improvement in exercise performance at 1 year compared with the medical group, and at 5 years exercise-induced ischemia as evidenced by S-T depression and exertional angina remained substantially decreased in the surgical group with little change in the medical group. However, the frequency and severity of exercise-induced ventricular arrhythmias in each group remained unchanged at 1 and 5 years from those at entry. Similar results were obtained from an evaluation of ventricular arrhythmias in the electrocardiogram at rest. With the exception of exercise-induced ventricular tachycardia and fibrillation, no relation was found between ventricular arrhythmias and sudden death.

Coronary bypass grafting does not decrease the frequency or severity of exercise-induced or resting ventricular arrhythmias. In patients with stable angina pectoris, with the exception of ventricular tachycardia and fibrillation, exercise-induced ventricular arrhythmias are poor predictors of sudden death. The data suggest that exercise-induced ventricular arrhythmias may not be related to ischemia but to other effects of exercise such as cardiac stimulation by catecholamines or other factors.

Ventricular premature complexes are a risk factor for sudden death in asymptomatic subjects and in patients with coronary artery disease.[1–4] Patients with coronary artery disease have a greater incidence of ventricular premature complexes than asymptomatic normal subjects.[4]

In previous reports from our laboratory it was shown that coronary bypass grafting in patients with stable angina did not reduce the incidence or severity of ventricular arrhythmias despite relief of exercise-induced myocardial ischemia. In addition, exercise related arrhythmias were not found to be predictors of sudden death.[5] This report extends these original observations in a larger group of patients followed up for 5 years.

Methods

Patients: All patients who were entered into a national randomized cooperative trial at the Palo Alto Veterans Administration Medical Center were evaluated. All patients were men who had stable angina of at least 6 months' duration. None had a history of recent myocardial infarction (less than 6 months). All were evaluated with coronary arteriography and were considered suitable for coronary bypass grafting. Other entry qualifications have been described elsewhere.[6]

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A total of 143 patients were entered into the study and 102 of these patients who had been followed up for 5 years or until death are included in this report. Medical therapy alone was assigned to 54 patients and surgical treatment to 48 patients. At 5 years seven medically treated patients had crossed over to surgical therapy (13 percent). The 5 year mortality rate was 42 percent (23 of 54) in the medical group and 31 percent (15 of 48) in the surgical group. This difference was not significant ($P < 0.08$).

Surgically treated patients: There was one operative death (2 percent) and four patients (8 percent) had a nonfatal perioperative infarct. At 1 year left ventricular angiography was performed in 38 patients (85 percent). At least one patent graft was present in 84 percent of patients, and 77 percent of all grafts were patent. At entry 30 percent of the group were taking propranolol and the mean daily dose for the entire group was 53 mg. At 5 years 30 percent were taking propranolol and the mean daily dose was 80 mg. No patient required other antiarrhythmic medication.

Medically treated patients: At entry, 35 percent of the medically treated patients were taking propranolol and the mean daily dose for the entire group was 56 mg. At 5 years 66 percent of the patients were taking propranolol (mean daily dose, 120 mg) and all required nitrates. No patient required any other antiarrhythmic medication.

Electrocardiograms at rest: Ventricular arrhythmias at rest were evaluated by a review of three or more consecutive 12 lead single channel electrocardiograms taken at entry and at 1 and 5 years. This method yielded a mean of 160 complexes or approximately 3 minutes of recording. All ventricular arrhythmias were noted and classified by an independent observer. Propranolol therapy was not discontinued.

Multistage, symptom-limited treadmill tests (Bruce protocol): These tests were performed in all patients at entry and at 1 and 5 years. Leads II or III and V_4, V_5 or V_6 were recorded using a two channel electrocardiograph during exercise and for at least 5 minutes after cessation of exercise. All ventricular premature complexes were counted and classified. Propranolol was discontinued 24 hours before the test in all patients.

The following classification system for ventricular arrhythmias was used: (1) Any ventricular premature complexes. (2) Frequent ventricular premature complexes (estimated at more than 10 beats/min). (3) Complex ventricular premature complexes. These included bigeminy, pairs, multifocal complexes, R on T complexes and ventricular fibrillation. In addition, the grading system proposed by Lown and Wolf[7] was used (Table I).

Follow-up: For each time period the mean values for all surviving patients are reported. Mean values for each time period for only those patients surviving at 5 years were also determined. There were no significant differences between these methods of calculation so the former method was used. *Medically treated patients who crossed over to surgery* are included in the medical group because excluding these patients did not change the results.

Sudden death was defined by the presence of all of the following three criteria: (1) The patient died of nontraumatic causes within 24 hours of the onset of symptoms. (2) The patient died outside the hospital. (3) The patient had not been hospitalized for acute myocardial infarction within 6 months of death.[8]

Data evaluation: The independent t test was used for comparison of continuous data (mean values) and Student's paired t test for comparison of values between groups. A P value of <0.05 was considered significant.

Results

Clinical characteristics: The entry characteristics of the study group are summarized in Table II. The medical group had a larger number of patients with triple vessel disease (70 versus 30 percent), and the surgical group had a greater number of patients with two vessel disease (44 versus 15 percent). The mean number of vessels involved was the same in both groups. No other significant differences between the two groups were evident.

Arrhythmia in electrocardiograms at rest: Data from the evaluation of the electrocardiograms at rest are summarized in Table III. At entry, 33 percent of the surgical group had ventricular premature complexes compared with 18 percent of the medical group. The surgical group had a slightly higher frequency of ventricular premature complexes and a higher grade of arrhythmia at entry than the medical group and this difference was present at 1 and 5 years. No difference in frequency or severity occurred at 1 and 5 years within each group.

Exercise performance: Exercise tests revealed a substantial improvement in performance in the surgically treated patients at 1 year compared with findings in the medically treated patients. This was accompanied by a significant reduction in pulmonary wedge pressure measured during exercise.[9] This difference was still

TABLE I

Exercise-Induced Ventricular Arrhythmias: Method of Grading*

Grade	Arrhythmia
0	No arrhythmias
1	Rare VPCs (≤1/100 beats)
2	Frequent VPCs (>1/100 beats)
3	Multiform VPCs
4	Couplets
5	Early VPCs (R-R′/Q-T <1)
6	Ventricular tachycardia
7	Ventricular fibrillation

* Modified from Lown and Wolf.[7]
VPCs = ventricular premature complexes.

TABLE II

Characteristics of Surgically and Medically Treated Patients at Entry

	Surgical Group	Medical Group	*P* Value
Patients (no.)	48	54	
Age (yr)	52 ± 7	51 ± 7	NS
Previous MI (%)	60	57	NS
Diseased vessels			
One	3 (6%)	8 (15%)	NS
Two	21 (44%)	8 (15%)	<0.005
Three	24 (50%)	38 (70%)	NS
Mean	2.44 ± .62	2.56 ± .74	NS
Ejection fraction (mean) (%)	69	65	NS
Ejection fraction <50% (%)	15	15	NS

NS = not significant; MI = myocardial infarction; *P* = probability.

TABLE III

Ventricular Arrhythmias in Resting Electrocardiogram at Entry and at 1 and 5 Year Follow-Up*

	Surgical Group	Medical Group	*P* Value
	Number of Complexes Reviewed		
Entry	168 ± 77	144 ± 79	NS
1 year	158 ± 65	151 ± 60	NS
5 years	182 ± 56	187 ± 54	NS
	VPCs/100 Complexes		
Entry	1.5 ± 3.6	1.1 ± 4.3	NS
1 year	1.5 ± 3.9	1.6 ± 4.7	NS
5 years	1.95 ± 6.1	1.0 ± 3.8	NS
	Arrhythmia Grade		
Entry	0.7 ± 1.1	0.4 ± 1.0	NS
1 year	0.6 ± 0.8	0.5 ± 1.0	NS
5 years	0.7 ± 0.9	0.5 ± 0.9	NS

* Values are expressed as mean ± standard deviation. NS = not significant; *P* = probability; VPCs = ventricular premature complexes.

evident at 5 years but to a lesser degree. Relief of ischemia in the surgical group was particularly significant, as shown by the decrease in angina and in S-T segment depression during exercise (Fig. 1 and 2). Medically treated patients exhibited little change in exercise performance or degree of exercise-induced ischemia at 1 and 5 years (Table IV).

Exercise-induced ventricular arrhythmias: These data are summarized in Table V. Again the surgical group had more arrhythmias, more frequent or complex arrhythmias and a higher mean grade of arrhythmia at entry and at 1 and 5 years. No significant change occurred from the entry status in either the surgical or the medical group. This is illustrated in Table VI in which changes in the arrhythmia grade are indicated for both study groups.

Graft patency: The effect of graft patency on the results was examined by an analysis of the data in four groups of patients: Group A, all grafts open (20 patients); Group B, at least one graft open (12 patients); Group C, all grafts closed (6 patients); and Group D, medically treated patients who had surgery (9 patients).

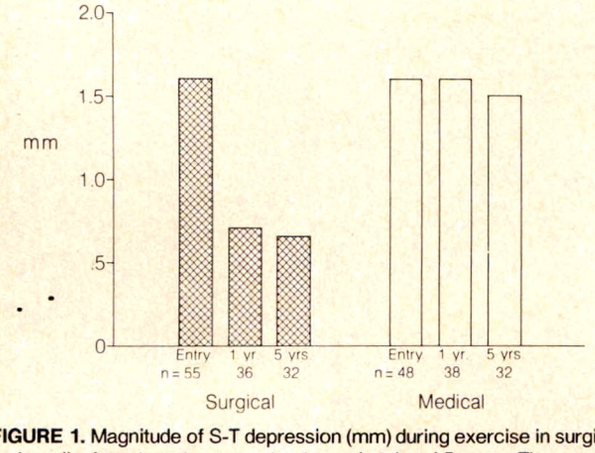

FIGURE 1. Magnitude of S-T depression (mm) during exercise in surgical and medical treatment groups at entry and at 1 and 5 years. The number (n) of patients studied at each interval is indicated below the bars.

TABLE IV

Exercise Performance of Surgically and Medically Treated Patients on Entry: 1 and 5 Year Follow-Up*

	Surgical Group	Medical Group	*P* Value
	Duration of Exercise (sec)		
Entry	321 ± 156	258 ± 149	<0.05
1 year	364 ± 124	232 ± 93	<0.001
5 years	385 ± 149	305 ± 150	<0.05
	Peak Heart Rate (per min)		
Entry	139 ± 21	132 ± 18	NS
1 year	147 ± 23	127 ± 20	<0.001
5 years	133 ± 28	130 ± 19	NS
	Peak Double Product†		
Entry	214 ± 57	194 ± 45	NS
1 year	240 ± 68	193 ± 48	<0.001
5 years	215 ± 66	205 ± 54	NS
	S-T Depression (mm)		
Entry	1.6 ± 1.2	1.6 ± 1.1	NS
1 year	0.7 ± 1	1.6 ± 1.1	<0.001
5 years	0.65 ± 0.8	1.5 ± 1.3	<0.005
	Angina During Test (% of patients)		
Entry	73	92	NS
1 year	26	81	<0.001
5 years	37	69	<0.005

* Values are expressed as mean ± standard deviation.
† Double product = (peak heart rate × systolic blood pressure)/100.
NS = not significant; *P* = probability.

No significant differences were found in ventricular arrhythmias at 1 year and at 5 years within these groups (Table VII).

Ventricular tachycardia or fibrillation in association with exercise: Five patients had such arrhythmias. In one medically treated patient ventricular tachycardia developed during the exercise test at entry.

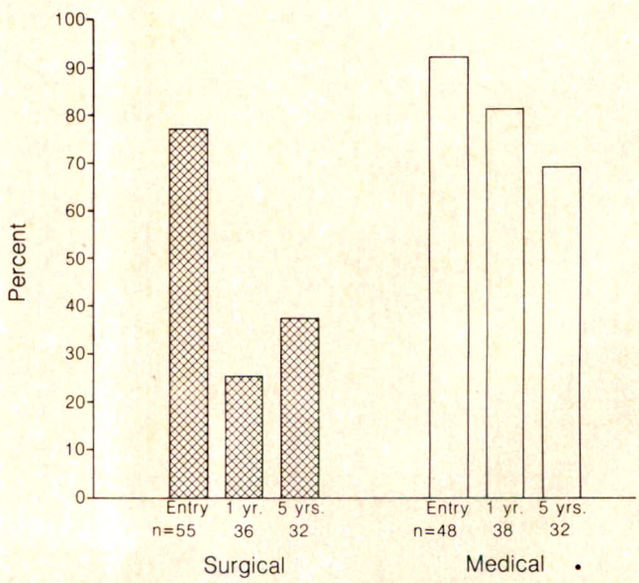

FIGURE 2. Incidence rates of angina (%) experienced during exercise in surgical and medical treatment groups at entry and at 1 and 5 years. The number (n) of patients studied at each interval is indicated below the bars.

TABLE V

Exercise-Induced Ventricular Arrhythmias on Entry and at 1 and 5 Year Follow-Up

	All Ventricular Arrhythmias		Frequent or Complex Ventricular Arrhythmias (≥Grade 2)		Arrhythmia Grade	
	Surgical Group	Medical Group	Surgical Group	Medical Group	Surgical Group	Medical Group
Entry	49% (no. = 55)	30% (no. = 48)	39%	20%	1.22 ± 1	0.6 ± 1
1 year	50% (no. = 36)	29% (no. = 38)	33%	18%	1.08 ± 1.1	0.4 ± 1
5 years	46% (no. = 33)	30% (no. = 32)	33%	9%	1.2 ± 1.1	0.6 ± 1.1
P value	NS	NS	NS	NS	NS	NS

NS = not significant; *P* = probability.

He had left main coronary artery disease and 8 months after entry had bypass graft surgery. At 1 year, exercise capacity had improved and no serious arrhythmias occurred. All three grafts were patent.

In three patients in the surgical treatment group ventricular tachycardia (two patients) or fibrillation (one patient) developed in association with exercise at 1 year. All three had demonstrated improvement in exercise capacity and had patency of all grafts. Two of these patients died suddenly 18 and 51 months, respectively, after the exercise-induced arrhythmias. The diagnosis of acute myocardial infarction was made at autopsy in each patient and all grafts were patent. The third patient is still alive and did not manifest serious arrhythmias during his 5 year test. A fourth patient had ventricular tachycardia during his 5 year exercise test; he had maintained moderate improvement in exercise capacity and had patency of all grafts.

Sudden death: Sixteen patients in the study group died suddenly. Data from these patients are compared with data in the remaining 84 patients who were either still alive (55 patients) or who had not died suddenly (Table VIII). There is no significant difference in ventricular arrhythmias except in the grade of arrhythmia, which is slightly higher in the surgical group. This is partly due to the two surgically treated patients who had serious ventricular arrhythmias at 1 year and died suddenly. If data from these patients are removed from Table VIII, there is no significant difference between the two groups.

TABLE VI

Changes in Grade of Ventricular Arrhythmia at 5 Years in the Surgically and Medically Treated Patients

Arrhythmia Grade	Surgical Group	Medical Group	*P* Value
Not changed	15 (45%)	17 (53%)	NS
Increased	8 (27%)	8 (25%)	NS
Decreased	10 (30%)	7 (22%)	NS

NS = not significant; *P* = probability.

TABLE VII

Changes in Grade of Ventricular Arrhythmia in the Surgically Treated Patients, Grouped by Graft Patency*

Grade of Arrhythmia	Group A (no. = 20)	Group B (no. = 12)	Group C (no. = 6)	Group D (no. = 7)
Not changed	27%	70%	40%	57%
Increased	30%	0%	20%	0%
Decreased	43%	30%	40%	43%

* Does not include patients who died before the 1 year follow-up.
Group A = all grafts patent; Group B = at least one graft patent; Group C = all grafts occluded; Group D = medical patients who had surgery.

Discussion

Possible limitations of study: Our study has several limitations:

1. Holter monitoring would have been a more accurate method of evaluating arrhythmias at rest but this method was not used at the time of entry. However, it has been shown that patients who exhibit ventricular arrhythmias in the electrocardiogram at rest usually have greater incidence of arrhythmias if continuous monitoring is used.[10,11] Patients who have no ventricular arrhythmias in the electrocardiogram at rest may show arrhythmias during ambulatory monitoring. de Soyza et al.,[12] using 6 hour monitoring in a similar randomized study, reported essentially the same results.

2. The numerical system used to classify ventricular arrhythmias may not be the best for evaluation of exercise-related arrhythmias. A simpler classification such as that proposed by Ruberman et al.[4] may be more applicable in the prediction of sudden death. However, most of the patients in our study who are classified as having frequent or complex arrhythmias or who have a high arrhythmia grade would be classified as having complex arrhythmias using the Ruberman system. Ruberman et al. found that complex arrhythmias were predictive of an increased incidence of sudden death.

TABLE VIII

Exercise-Induced Ventricular Arrhythmias: Patients Who Died Suddenly Compared With All Other Patients

Patients	All Ventricular Arrhythmias	Frequent or Complex Ventricular Arrhythmias (≥Grade 2)	Arrhythmia Grade*
Sudden death (no. = 18)	44%	33%	1.5 ± 1.1
All others (no. = 84)	38%	28%	0.86 ± 1.0
P value	NS	NS	<0.05

* Mean ± standard deviation.
NS = not significant; *P* = probability.

3. The number of patients studied is small and firm conclusions cannot be made regarding the relation between exercise-related ventricular arrhythmias and sudden death.

Advantages of a randomized study: A randomized study comparing medical versus surgical treatment is useful because significant changes in ventricular arrhythmias could have occurred over the 5 year follow-up period in the medical group. For example, arrhythmias could have changed because of the greater use of propranolol or because of unrelieved ischemia. Our study has shown that neither surgical nor medical treatment changes the incidence or complexity of ventricular arrhythmias when the effect of propranol is excluded.

At entry, the surgical group had more ventricular arrhythmias and more complex arrhythmias than the medical group. This difference may have been related to the larger number of patients in the surgical group who had two vessel disease. Such differences may occur in randomized studies when the number of patients is small and stratification is not used. However, within each study group no changes in ventricular arrhythmias were noted at 1 and 5 years.

Comparison with previous studies: The results of this study are comparable with those of a similar randomized study by de Soyza et al.[12] who used 6 hour continuous monitoring at entry and at 1 year. Propranolol was not discontinued in their study. Only 22 percent of their surgically treated patients were taking propranolol compared with 95 percent of their medically treated patients. There was no difference in the incidence of arrhythmias at 1 year except for a slightly lesser incidence of complex arrhythmias in the medical group. This difference could have been due to propranolol.[13] Guinn and Mathur[14] noted no difference in ventricular premature complexes at 1 year in a similar randomized study.

In the study by de Soyza et al.[12] no relation was evident between ventricular ectopic activity and sudden death. Only five patients in that study died suddenly. The results of our study are similar except for the occurrence of ventricular tachycardia or ventricular fibrillation during exercise in five patients. Previous reports[1,3,4,15–17] have shown a relation between ventricular premature complexes, prognosis and sudden death but the patient groups studied are not comparable.

There are many published reports of the effect of coronary bypass surgery or aneurysmectomy, or both, on ventricular arrhythmias.[18–22] Such reports are difficult to evaluate because of the lack of appropriate control groups. Most of the patients in such studies have had recurrent, serious ventricular arrhythmias and are not comparable with the patients in this study, none of whom had a ventricular aneurysm.

Clinical implications: Our data show that, in patients with stable angina, bypass graft surgery is not associated with any change in ventricular premature complexes or complex ventricular arrhythmias at rest or during exercise over a 5 year follow-up period despite evidence of substantial relief of exercise-induced ischemia persisting for 5 years. In addition, ventricular arrhythmias were not predictive of sudden death except in five patients who had ventricular tachycardia or ventricular fibrillation during exercise. Such exercise-induced arrhythmias would appear to have a poor prognosis.

These data suggest that ventricular arrhythmias at rest or during exercise in patients with angina may not primarily be related to ischemia but to other unknown factors. Other investigators[23] have shown that serious ventricular arrhythmias are rare in patients with unstable angina compared with patients with recent myocardial infarction. Electrical instability during exercise may be increased by factors other than ischemia such as catecholamine release. This phenomenon merits further investigation.

Acknowledgment

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Detection of Left Ventricular Functional Reserve by Supine Exercise Hemodynamics in Patients With Severe, Chronic Heart Failure

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Hemodynamic changes during exercise were evaluated in 20 patients with severe, chronic congestive heart failure. Two groups were identified by their stroke work response to maximal exercise. Group I (eight patients) showed an increase in stroke work index. This occurred because the stroke volume increased and the difference between mean systolic pressure and left ventricular filling pressure increased. Group II (12 patients) showed a decrease in stroke work index. This occurred because stroke volume decreased while the difference between mean systolic pressure and left ventricular filling pressure did not change. Despite hemodynamic differences, the groups could not be distinguished by the usual clinical criteria for heart failure including etiology, New York Heart Association functional class, heart size on chest X-ray film or duration of heart failure. Clinical criteria are relatively insensitive in predicting the exercise hemodynamics of any given patient with chronic severe heart failure. Determining the exercise hemodynamics may be helpful as a means of assessing left ventricular functional reserve in heart failure. Prognostic implications, drug therapy and prescription of activities may require adjustment based on this spectrum of hemodynamic response to exercise in patients with chronic heart failure.

Determination of resting hemodynamics provides valuable information regarding the severity of depressed cardiac function in patients with both acute and chronic heart failure. However, evaluation of cardiac function only at rest without considering changes induced during exercise does not allow for the complete assessment of function. The vast majority of patients with chronic heart failure may remain relatively symptom-free at rest and may experience their limiting symptoms only during exercise. It is therefore desirable to evaluate not only resting cardiac function but also changes in cardiac performance during exercise.[1,2] Although some information is available regarding hemodynamic changes during exercise in patients with chronic heart failure of mild or moderate severity, such changes in patients with severe or advanced heart failure have not adequately been investigated. The purpose of this study was to evaluate changes in hemodynamics during exercise in a group of patients with severe chronic congestive heart failure.

Methods

Patients: Twenty patients with New York Heart Association class III or IV congestive heart failure[3] were selected from both inpatient and outpatient groups. The clinical history, physical examination, electrocardiogram and chest X-ray film were utilized to determine the cause of heart failure along with data from right heart catheterization (20 patients), left heart catheterization (11

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TABLE I

Patient Data

Case no.	Age (yr) & Sex	NYHA Class	Etiology	Work Load (kilopond-meters)	SWI (g·m·m²)		CI (cc/min per m²)		HR (beats/min)		SVI (ml/beats per m²)		MSP (mm Hg)		LVFP (mm Hg)		Ex FAC (ml/100 per ml $\dot{V}O_2$)
					Rest	Ex	Rest	Ex	Rest	Ex	Rest	Ex	Rest	Ex	Rest	Ex	
Group I																	
1	24F	III	CM	200	20	28	1.67	2.40	96	103	18	23	86	89	10	15	—
2*	45F	IV	CM	150	15	21	1.36	2.20	67	75	20	30	81	81	28	28	650
3	64M	IV	CAD	150	39	52	2.32	3.08	85	135	27	23	152	146	20	20	770
4*	55M	IV	CAD	150	13	28	1.66	2.70	76	90	22	30	103	138	27	32	770
5	77M	IV	CAD	100	40	54	1.10	2.04	96	111	12	18	145	178	23	28	—
6	44M	III	CM	400	27	43	2.19	2.74	90	104	24	26	107	162	15	30	620
7	46M	III	CM	300	15	28	1.78	3.46	84	132	21	26	86	126	22	35	400
8	67M	III	CAD	200	32	39	1.71	2.94	103	132	17	22	132	171	32	45	90
Aver				206	25	37	1.73	2.70	87	110	20	25	112	136	22	29	550
±SE				±35	±4	±4	±0.14	±0.17	±4	±7	±2	±1	±10	±13	±3	±3	±107
Group II																	
9*	44F	III	CAD	100	24	22	1.98	2.32	80	105	25	22	87	104	15	28	—
10	53M	III	CAD	200	18	20	1.85	2.75	90	114	21	24	100	110	35	50	440
11*	67M	IV	CAD	200	37	31	1.85	2.88	77	123	24	23	131	130	20	35	—
12*	52F	IV	CM	100	16	15	1.65	1.73	93	108	20	17	89	99	24	33	—
13	66F	IV	CM	50	15	15	1.75	1.91	104	148	18	16	102	124	35	40	250
14	71F	IV	CAD	100	40	29	1.89	2.16	57	96	17	13	112	144	18	49	—
15	56M	III	CM	250	29	30	1.87	2.78	68	112	31	23	111	119	20	30	350
16	73F	IV	CAD	100	29	23	3.11	3.24	88	120	28	25	97	112	38	50	170
17*	59M	III	CAD	300	48	31	2.48	2.88	81	116	36	27	127	139	12	48	220
18	63M	III	CAD	200	42	21	2.31	2.46	75	132	31	25	120	123	19	42	80
19	58M	IV	CM	300	24	23	2.47	3.09	140	164	31	19	117	126	16	35	250
20	66M	III	CM	150	16	18	1.48	1.71	76	100	18	19	83	108	23	30	200
Aver				171	28	23	2.06	2.49	86	120	25	21	106	120	23	39	245
±SE				±24	±3	±2	±0.13	±0.15	±6	±2	±1	±5	±4	±4	±2	±2	±39

* Mortality since study.

Aver = average; CAD = coronary artery disease; CM = idiopathic cardiomyopathy; CI = cardiac index; Ex = exercise; Ex FAC = exercise factor (that is, change in cardiac output/change in oxygen uptake); HR = heart rate; LVFP = left ventricular filling pressure; MSP = mean systolic pressure; NYHA = New York Heart Association functional classification; SVI = stroke volume index; SE = standard error; SWI = stroke work index.

patients), M mode or two dimensional echocardiography, or both (18 patients) and scintigraphic wall motion analysis (8 patients).

The study group had the following characteristics: (1) severe left heart failure of at least 6 months' duration with either cardiomyopathic or coronary artery disease as a cause; (2) stable congestive heart failure, defined as no episodes of acute pulmonary edema within the previous 10 weeks; (3) treatment with stable doses of digoxin and diuretic drugs; (4) moderate to severe impairment of exercise tolerance despite this medical therapy; and (5) normal musculoskeletal function. Except for three patients, the ejection fraction as measured by echocardiogram or radionuclide imaging of wall motion was diminished, ranging between 14 and 42 percent.

Measured hemodynamic variables: A triple lumen Swan-Ganz thermodilution catheter[4] was inserted percutaneously for determination of right atrial, pulmonary arterial and pulmonary capillary wedge pressures. Cardiac output was determined in triplicate with the thermodilution technique. Heart rate measured from the electrocardiogram was determined simultaneously with cardiac output measurements. Arterial blood pressure was measured with use of an arterial cannula inserted percutaneously into the radial artery in 16 patients and with use of sphygmomanometry of the brachial artery in the other patients. Blood oxygen saturation levels were determined from blood gas analysis (Corning, Medfield, Massachusetts)[5] and verified with oxygen content determinations.[6]

Calculated hemodynamic variables: Stroke volume index, stroke work index, arterial-mixed venous oxygen difference and oxygen consumption were calculated from the measured variables as follows: (1) SVI = CO/HR/BSA, where SVI is stroke volume index in ml/beat per m^2, CO is cardiac output in liters/min, HR is heart rate in beats/min and BSA is body surface area in m^2; (2) SWI = 0.0136 × SVI × (MSP–LVFP), where SWI is stroke work index in gm·m/m^2, MSP is mean systolic pressure in mm Hg calculated as 0.8 × pulse pressure + diastolic pressure, and LVFP is the left ventricular filling pressure as either the pulmonary capillary wedge pressure or pulmonary arterial end-diastolic pressure. The method of determining filling pressure was constant in each patient. The pulmonary capillary wedge pressure has been shown to be a good estimate of the left ventricular end-diastolic pressure both at rest and at exercise with the assumption that there is no mitral valve or pulmonary venous obstruction[7,8]; (3) a-vO_2 = (a_{SAT} − v_{SAT}) × Hgb × 1.34, where a-vO_2 is the arterial-mixed venous oxygen saturation difference, a_{SAT} is the radial arterial blood oxygen saturation, v_{SAT} is mixed venous oxygen saturation obtained from the pulmonary arterial blood, Hgb is hemoglobin concentration in g/dl, and the factor 1.34 is the oxygen capacity of 1 g of hemoglobin. This factor agreed with the oxygen-carrying capacity·measurements performed in our laboratory.

Protocol: Hemodynamic measurements were made after 15 minutes of quiet rest with the patient recumbent. After these determinations, the patient's legs were raised and secured to the bicycle ergometer pedals. Exercise was initiated at 100 kilopond-meters (except in one class IV patient, where exercise was begun at 50 kilopond-meters). Work load was increased by 50 kilopond-meters every 3 minutes. Bicycle pedaling was performed at 40 revolutions/min by synchronizing exercise with a metronome (1.3 hertz). All patients exercised to exhaustion. At maximal exercise levels achieved, all patients also experienced dyspnea. In one patient, angina and fatigue were responsible for discontinuation of exercise. No other patient experienced chest pain, electrocardiographic S-T changes of ischemia, arrhythmias or pulmonary edema.

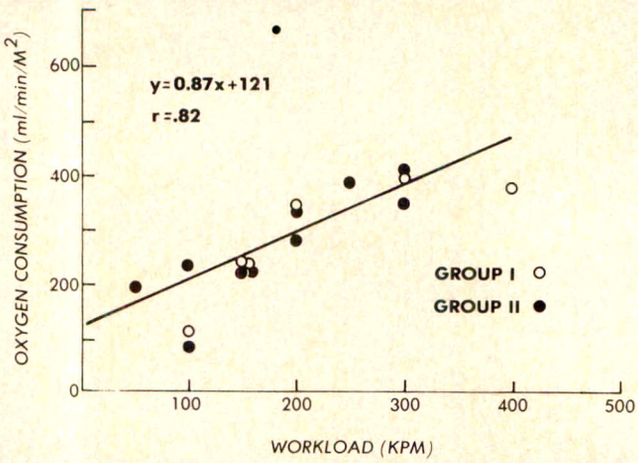

FIGURE 1. Correlation of oxygen consumption with maximal work load in each patient. Although work load and oxygen uptake were tightly coupled, the patients were subsequently classified according to hemodynamic response. KPM = kilopond-meters; M^2 = square meters; r = correlation coefficient.

Hemodynamic variables were measured during exercise. When the patients reported that they were near their subjective maximal level of exercise, all measurements were made within a 2 minute period at peak exercise.

Data analysis: Data were paired in each patient as resting and exercise data. Eight patients with an increase in stroke work index greater than 15 percent during exercise were arbitrarily grouped together and called Group I. Twelve patients with a less than 15 percent increase in stroke work index from rest to exercise constituted Group II. We utilized an analysis of covariance statistic for testing the significance of changes in variables from rest to exercise between groups. This allowed for comparison of change between groups with adjustment for differences in baseline values. Differences at or less than the 0.05 level ($P < 0.05$) were considered significant.

Results

Resting hemodynamics: Table I contains the hemodynamic data of all patients. At rest, each patient had a decreased stroke work index compared with the normal index (27.0 ± 2.4 g·m/m^2, mean ± standard error) and all but two had an increased left ventricular filling pressure compared with the normal value (22.6 ± 1.8 mm Hg).

Exercise oxygen uptake and hemodynamics: During exercise, the patients exhibited the expected significant correlation between peak external work load (E, kilopond-meters) and maximal oxygen uptake ($\dot{V}O_2$, ml/min fm^2) according to the equation: $\dot{V}O_2$ = 0.87 E + 121 (r = 0.82, $P < 0.01$, Fig. 1). However, during exercise, the patient group exhibited nonuniform hemodynamic changes (Fig. 2). Although the average change was a small increase in stroke work index to 28.6 ± 2.5 g·m/m^2 and a large increase in left ventricular filling pressure to 35.2 ± 2.2 mm Hg the responses among patients was quite variable.

Comparison of the two groups: To further analyze cardiac performance during exercise, we subdivided the patients into two groups on the basis of percent change in stroke work index. Group I was composed of eight

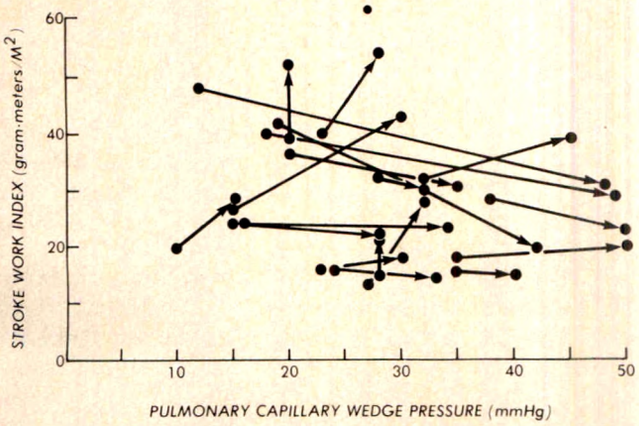

FIGURE 2. Relation of stroke work index to pulmonary capillary wedge pressure at rest and at maximal symptom-limited exercise in all patients studied. **Tail of arrow** is at rest, and **head of arrow** is at exercise.

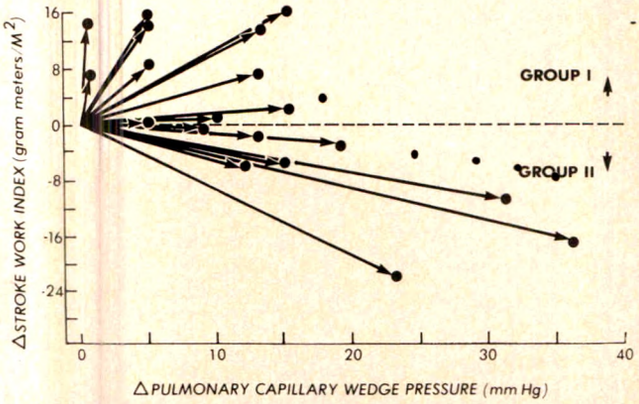

FIGURE 3. Change in stroke work index versus change in pulmonary capillary wedge pressure from rest to peak exercise in all patients. **Dashed line** indicates no change in stroke work index. Group I comprises patients who increased stroke work index more than 15 percent above the value at rest. Patients in Group II had less than a 15 percent increase or a decrease in stroke work index compared with the value at rest.

patients whose stroke work index increased more than 15 percent with exercise. The 12 patients in Group II had a less than 15 percent increase or a decrease in stroke work index with exercise (Fig. 3). The mean stroke work index increased in Group I by 12 g·m/m^2 and decreased in Group II by 5 g·m/m^2, as one would expect from the definition of the groups in our study. To examine the reasons for changes in stroke work index during exercise, we compared the component changes (that is, stroke volume index, mean systolic pressure and left ventricular filling pressure) in the two groups (Fig. 4). Stroke volume increased in Group I by 5 ml/beat per m^2 and decreased in Group II by 3 (P <0.02). Mean systolic pressure increased in Group I by 24 mm Hg and similarly increased in Group II by 14 (P >0.2). Left ventricular filling pressure increased in Group I by 7 mm Hg and increased in Group II by 16 (P <0.01). The exercise factor, defined as the increase in cardiac output divided by the increase in oxygen uptake, was 500 ml/100 ml $\dot{V}O_2$ in Group I and 245 in Group II (P <0.02). This factor serves to quantify the oxygen delivery capacity of the heart. A larger number would indicate an increased oxygen consumption with exercise related to increased flow versus increased oxygen extraction.

Despite very different hemodynamic responses to exercise in the two groups, there were no clinical or hemodynamic differences at rest between the groups. Age,

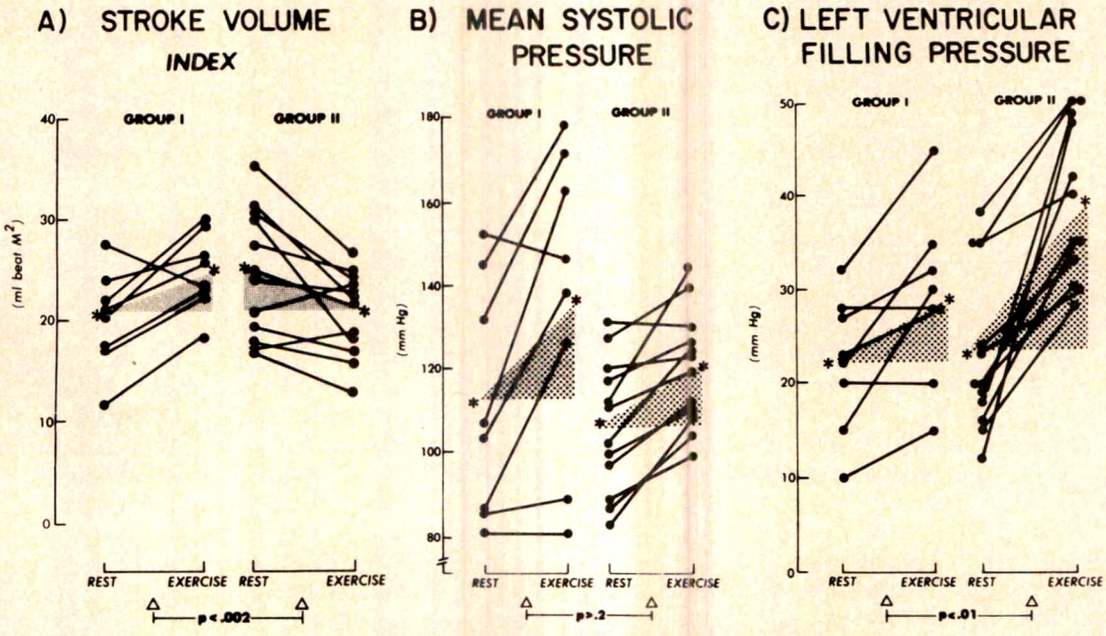

FIGURE 4. Changes in variables from rest to exercise for patients in Groups I and II. **A,** stroke volume index; **B,** mean systolic pressure; **C,** left ventricular filling pressure. **Hatched areas** show average change from rest to exercise.

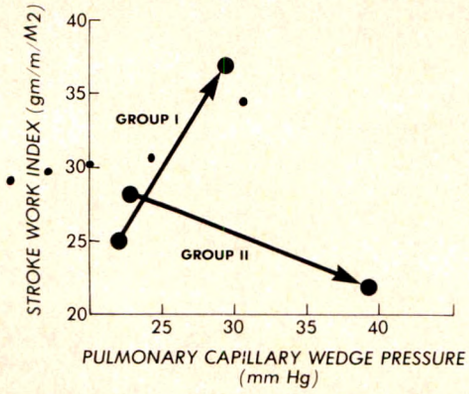

FIGURE 5. Mean resting and exercise stroke work index and pulmonary capillary wedge pressure for Groups I and II.

ratio of men to women, left ventricular filling pressure and stroke work index at rest, ratio of patients with cardiomyopathy versus coronary artery disease, duration of heart failure, degree of cardiomegaly by chest X-ray film, New York Heart Association functional class and peak work load were essentially the same in the two groups. Only one patient had a history of angina in the 6 months before the study. This patient was in Group I, the group in which stroke work index could be increased with exercise. The short-term mortality rate (12 month mean follow-up) was similar in both groups; 2 of 8 patients in Group I and 4 of 12 in Group II died (Table I). The patients in both groups were treated with the same medical regimen during this period, including vasodilator therapy.

Discussion

Changes in hemodynamics during exercise provide important information concerning the ability of the cardiovascular system to meet increased demands.[9] In the absence of pericardial and valve lesions, the ability of the heart to meet the demands of exercise might be conceptualized as reflecting reserve ventricular performance. The augmentation of ventricular function that occurs with exercise is the result of increased sympathetic tone, the Frank-Starling mechanism[10,11] and the small inotropic effect of increased heart rate.[12] For this study we chose stroke work index as an approximation of left ventricular function because it is a useful measure of external work performed by the left ventricle. The normal response to exercise is a large increase in stroke work index.[13–16]

Stroke work response to exercise: On exercise, patients with myocardial disease and class III or class IV failure reveal a spectrum of hemodynamic responses.[17] The exercise hemodynamics of our patients could not be characterized by any single response. Therefore, we found it convenient to divide responses into two groups (Fig. 5): patients whose stroke work increased (Group I) and patients whose stroke work did not increase (Group II). From the variables that compose the calculation, changes in stroke work are proportional to changes in stroke volume and to changes of the difference between mean systolic pressure and left ventricular filling pressure. Patients in Group I had increased stroke work because stroke volume increased and because the difference between mean systolic pressure and left ventricular filling pressure increased. Patients in Group II had decreased stroke work because stroke volume decreased and the difference between mean systolic pressure and left ventricular filling pressure did not change.

This spectrum of hemodynamic response could not be predicted from the hemodynamics at rest. At rest, stroke work index was diminished and left ventricular filling pressure was increased in all patients, but changes during exercise were frequently dissimilar between patients. For example, at rest, Patients 3 and 18 had essentially the same stroke work index (39 versus 41 $g \cdot m/m^2$) and left ventricular filling pressures (20 versus 19 mm Hg). With exercise, Patient 3 had an increase in stroke work index to 52 $g \cdot m/m^2$ without a change in left ventricular filling pressure, whereas Patient 18 had a decrease in stroke work index to 21 $g \cdot m/m^2$ with an increase in filling pressure to 42 mm Hg.

Although the two groups did not differ in stroke work index and filling pressure at rest, they differed with exercise. Compared with Group II, Group I had a higher stroke work index with lower level of filling pressure at peak exercise, and these findings suggest a better ventricular performance. This ventricular reserve could be unmasked only by exercise hemodynamics.

Correlation with clinical characteristics: The spectrum of hemodynamic response could not be predicted from the clinical classification of the patients, contrary to what might be expected.[13] Patients with class IV heart failure, as well as those with class III failure, showed a spectrum of response. In other words, both Group I and II had the same ratio of patients with class III and IV failure. Also, no other distinguishing clinical characteristics could be found by physical examination, by age, ratio of men to women, ratio of patients with cardiomyopathy to patients with coronary artery disease, duration of heart failure or degree of cardiomegaly by chest X-ray film.

Factors determining maximal symptom-limited exercise tolerance: Despite a better ventricular reserve, the patients in Group I did not exercise more than those in Group II. The increased filling pressures were not clinically detectable from the degree of dyspnea. One might conclude that factors other than ventricular reserve determine maximal symptom-limited exercise tolerance. Because delivery of oxygen might be important, we calculated oxygen consumption from cardiac output and arteriovenous oxygen difference. Both groups had a similar oxygen consumption during exercise, and this consumption was proportional to work load. Patients in Group I had a larger cardiac output, whereas those in Group II had a wider arteriovenous oxygen difference. The partition of oxygen uptake into its two components may also be examined by calculation of the exercise factor.[17] Group I had normal exercise factors whereas Group II had low exercise factors. In other words, Group II represents patients with less

blood flow and more oxygen extraction than the patients in Group I because oxygen consumption was similar in the two groups at any given work load (Fig. I). Patients in Group I should have been able to exercise further as a result of widening of the arteriovenous oxygen difference. We do not know why these patients did not utilize this potential source of oxygen, although it is possible that changes in peripheral tissue metabolism may accompany heart failure.

Clinical implications: Our study suggests that there is a spectrum of hemodynamic responses to exercise in patients with severe heart failure. The type of hemodynamic response cannot be predicted on the basis of clinical data routinely available. Exercise hemodynamic determinations may need to be done for the selection of appropriate therapy for heart failure. For example, patients whose left ventricular filling pressure is greatly increased with exercise may be a group in whom venodilator therapy would be most useful. Our study was performed in the supine position; sitting or standing exercise might yield different hemodynamic responses.[8]

What is the appropriate level of activity for patients with chronic heart failure? Many patients with heart failure are asymptomatic at rest but have symptoms with exercise. For this reason, physicians might tend to limit the activity of all patients with advanced heart failure. But not all patients symptomatic with exercise have adverse hemodynamic responses with exercise. Perhaps activity limitations should be prescribed only for those patients who are without the necessary ventricular reserve as determined from exercise hemodynamics.

In the groups studied there was no difference in prognosis, but the number of patients studied was small. Subtle differences in prognosis in relation to the exercise response might not be apparent until a larger group is followed up.

Ventricular reserve could be a factor in a patient's ability to withstand other forms of stress besides exercise such as the stress of cardiac and general surgery. Exercise hemodynamic measurements may be helpful in identifying ventricular functional reserve and therefore may be helpful in determining a patient's ability to tolerate surgery. This possibility requires further investigation.

The data presented were acquired with the patients recumbent and may not reflect the hemodynamic changes during standing. However, the analysis of ventricular function holds regardless of position. Because of recumbency and elevation of legs at the time of study, changes in filling pressure on exercise may have shown a greater increase than they would with standing exercise.

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Relation Between the Precordial Projection of S-T Segment Changes After Exercise and Coronary Angiographic Findings

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The recent introduction of electrocardiographic mapping permits measurement of the precordial area and severity of exercise-induced S-T segment changes. This study was designed to compare this technique with a modified 12 lead electrocardiogram in defining the degree and site of coronary artery disease. One hundred patients, who later had diagnostic coronary arteriography, underwent an exercise test using both 16 point precordial mapping and a modified 12 lead electrocardiogram. The sensitivity of electrocardiographic mapping (96 percent) for the diagnosis of coronary artery disease was significantly greater than that of the modified 12 lead electrocardiogram (80 percent). However, the specificity of the two lead systems was similar. Typical precordial projections of S-T segment change were found when the left main stem or proximal left anterior descending coronary artery were narrowed or when there was isolated disease of the left anterior descending or right coronary artery. Widespread precordial changes were found in patients with three vessel disease. Although there was no significant difference in the sensitivity (66 percent) and specificity (100 percent) of electrocardiographic mapping and of the 12 lead system in identifying three vessel disease, there was a significant difference in sensitivity (electrocardiographic mapping 74 percent, 12 lead system 42 percent) in identifying isolated single vessel disease. In addition, information regarding the presence of left main stem or proximal left anterior descending coronary arterial narrowing was obtained only with electrocardiographic mapping.

The superiority of electrocardiographic mapping over the modified 12 lead electrocardiogram has been shown, and clinical application of this technique should be useful in the management of patients presenting with chest pain.

It is important to the management of patients presenting with chest pain to have available a simple noninvasive test that will accurately identify those with ischemic heart disease. The exercise electrocardiogram has now become a standard diagnostic tool in these circumstances, and refinements in both the amount of exercise performed using a treadmill or bicycle ergometer and the lead systems used have greatly enhanced the value of this test.[1] However, a sizable number of false negative exercise tests are still found when the results are correlated with coronary arteriography.[2,3] Recently a simple, inexpensive method for recording precordial surface maps of the electrocardiogram after exercise was described.[4,5] This technique uses routine electrocardiographic equipment and permits measurement of the precordial area, severity and time course of electrocardiographic signs that occur after exercise. In addition, it is likely that recording from all over the chest will permit identification of precordial areas of S-T segment change that are not evident in the 12 lead exercise test. This study was undertaken to assess whether the precordial projection of S-T segment changes can be used to determine

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the severity of coronary arterial narrowing and to show the superiority of this technique over conventional exercise electrocardiography.

Methods

Patients: One hundred consecutive patients (84 men, 16 women) were studied before they underwent diagnostic coronary arteriography for the evaluation of chest pain. They were aged 32 to 63 years (mean 55.4). Administration of drugs, such as beta receptor antagonists and digitalis, known to influence the S-T segment was stopped at least 48 hours before the exercise test. All patients underwent 16 point precordial electrographic mapping before, during and for 10 minutes after exercise using a technique previously described.[4,5] Graded maximal exercise tests were performed with use of a bicycle ergometer. In addition, for the purposes of comparing the results with the conventional 12 lead electrocardiogram, the standard (I, II, III) and augmented (aVR, aVL, aVF) limb leads were recorded before, during and at each time period after exercise. Five of the precordial positions covered the area on the chest usually occupied by the six chest (V) leads and were selected to serve as the chest leads. One of the positions corresponded exactly to that of lead V_5.

All patients had left ventricular angiograms and coronary arteriograms performed with the Judkins technique.[6] The radiologists and cardiologists who performed the investigation also interpreted the coronary arteriograms without knowledge of the exercise tests.

Interpretation of the records: At each of the 16 positions the S-T segment changes were measured in three complexes and an average was taken. In each patient either the T-P or the P-Q segment was used as the isoelectric line. The choice depended on which of these remained identifiable before and after exercise. S-T segment depression was measured in millimeters to the nearest 0.5 mm. The S-T segment was considered depressed if there was a change of 1.0 mm or more lasting for 0.08 second or longer.[7,8] S-T segment elevation was measured 0.06 second from the end of the QRS complex and was considered elevated if there was a change of 1.0 mm or more. Contour maps of the area of S-T segment change were drawn for each precordial surface map.[9] The 16 precordial positions were divided into three areas (anterior, inferior and lateral) so that the results could be conveniently analyzed (Fig. 1). All data from the exercise tests were reported before the coronary arteriograms were obtained.

Statistical analysis was performed using paired t tests and chi square tests.

Results

Satisfactory recordings were obtained in all patients. The maximal heart rates achieved were 115 to 175 beats/min (mean 132.2 beats/min). The work load achieved was 12,000 to 68,500 watt seconds (mean 31,883 watt seconds), and exercise was continued for 5.8 ± 1.8 minutes (mean ± standard deviation).

The findings at coronary arteriography are shown in Table I. Eighty of the 100 patients had significant narrowing (70 percent) or more of luminal diameter of one or more major coronary arteries.

Electrocardiographic mapping: Seventy-seven of the 80 patients with significant coronary arterial narrowing had S-T segment changes on electrocardiographic mapping (sensitivity 96 percent). Two of the 20 patients with normal or nonsignificant narrowing of the major coronary arteries (less than 70 percent) had significant S-T segment changes in the surface map (specificity 90 percent).

Figures 2 and 3 show the relation between the precordial area (expressed as the mean number of positions with S-T segment change) and severity (expressed as the S-T segment change in millimeters for the 16 positions) and the number of vessels found to have significant narrowing on coronary arteriography. The area and severity of these electrocardiographic signs were greater in those patients with narrowing of three major coronary arteries than in those with only one or two vessel disease ($P < 0.01$). A similar result was found when patients with two vessel disease were compared with those in whom only a single vessel was narrowed ($P < 0.01$).

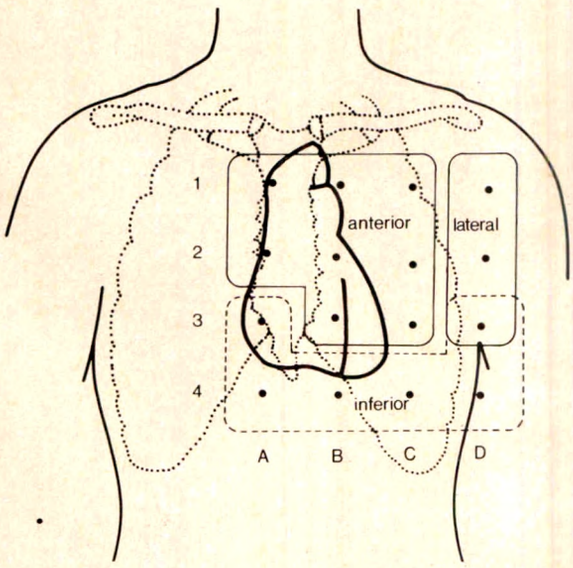

FIGURE 1. The 16 precordial positions have been divided into three areas: anterior, inferior and lateral.

TABLE I

Results of Coronary Arteriography in 100 Patients

	Cases (no.)
Single vessel disease	
LAD alone	12
LCx alone	2
RCA alone	5
Total	19
Two vessel disease	
Left main stem	6
LAD + LCx	9
LAD + RCA	12
RCA + LCx	2
Total	29
Three vessel disease	
Left main stem + RCA	6
LAD + LCx + RCA	26
Total	32
Normal or near normal coronary arteries	20

LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

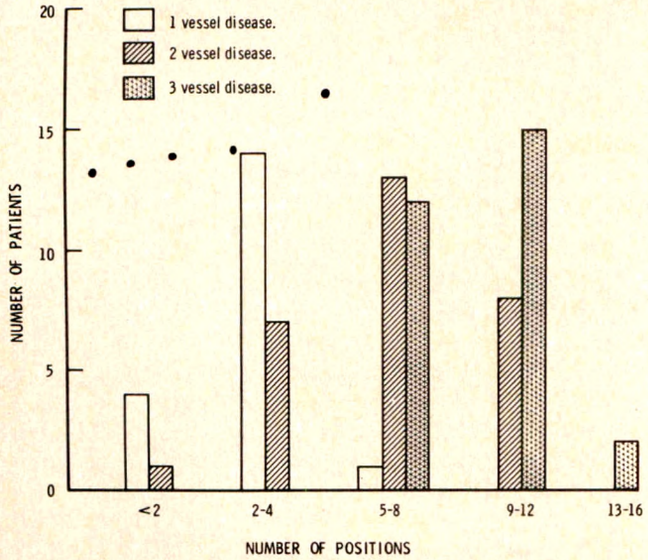

FIGURE 2. Maximal area (expressed as number of precordial positions) with S-T segment change after exercise correlated with the number of major coronary arteries found to be significantly narrowed on coronary arteriography.

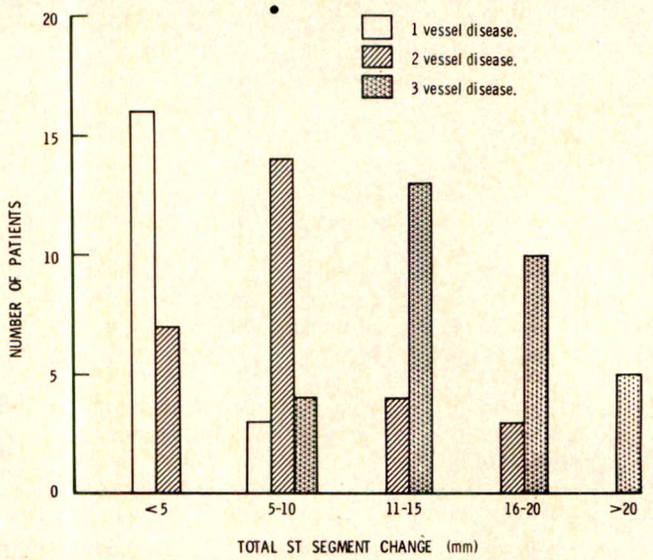

FIGURE 3. Maximal severity of S-T changes (expressed as the total S-T change in millimeters for the 16 leads) after exercise correlated with the number of major coronary arteries found to be significantly narrowed on coronary arteriography.

Table II lists the precordial areas of S-T segment changes involved in the 80 patients with coronary artery disease. Typical precordial projections were found confined to the anterior areas of the surface map when the left anterior descending coronary artery was involved alone (Fig. 4), to the inferior areas of the surface map when the right coronary artery was involved alone (Fig. 5) and to the lateral areas when the left circumflex artery was involved alone. However, in two patients more extensive areas of the precordium were involved although only one vessel was narrowed. Twenty-one patients (66 percent) with involvement of all three coronary arteries had electrocardiographic signs of ischemia after exercise in all the defined sites of the precordial map (Fig. 6), a finding not seen when the left or right coronary artery was involved alone (Table II).

Precordial projections of S-T segment change that involved the first row of the anterior region of the surface map (row 1, Fig. 1) were highly specific for the presence of either proximal left anterior descending coronary arterial narrowing (proximal to the first diagonal branch) or narrowing of the left main stem. Figure 7 shows a sequence of contour maps obtained from a patient with isolated proximal left anterior descending coronary arterial narrowing. The S-T segment

TABLE II

Site of S-T Segment Changes in Relation to the Findings on Coronary Arteriography in 80 Patients

Vessel Affected	No Changes	Site of S-T Changes						
		Ant	Lat	Inf	Ant + Lat	Ant + Inf	Inf + Lat	Ant + Lat + Inf
One Vessel Disease (no. = 19)								
LAD	2	8	...	...	2	...	...	...
LCx	...	...	2	...	...	...	...	...
RCA	...	1	...	4	...	...	...	...
Two Vessel Disease (no. = 29)								
LAD + LCx	1	1	...	...	4	3	...	...
LAD + RCA	...	4	...	1	1	5	1	...
RCA + LCx	...	...	...	...	1	...	1	...
LMCA	...	...	...	...	4	2	...	...
Three Vessel Disease (no. = 32)								
LAD + LCx + RCA	...	...	...	...	1	7	...	18
LMCA + RCA	...	...	...	...	1	2	...	3

Ant = anterior; Inf = inferior; LAD = left anterior descending coronary artery; Lat = lateral; LCx = left circumflex coronary artery; LMCA = left mainstem coronary artery; RCA = right coronary artery.

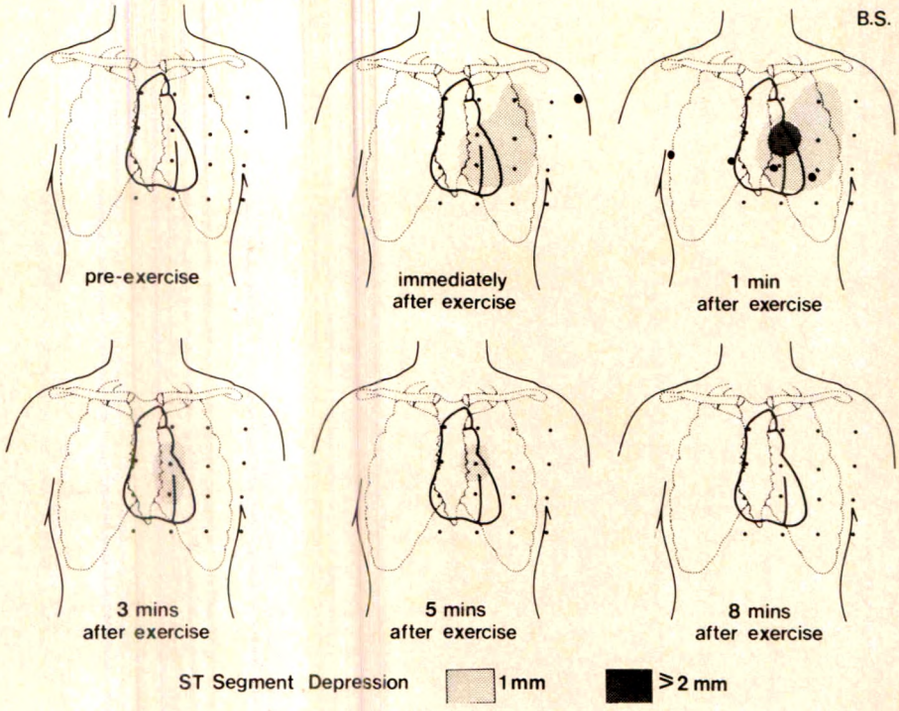

FIGURE 4. Typical sequence of contour maps of the areas of S-T segment depression in a patient with isolated left anterior descending coronary artery disease. The area of S-T segment depression is localized to the anterior regions of the surface map.

depression recorded after exercise is seen to involve only row 1 (Fig. 1). Forty-four patients had S-T segment changes involving this site (5 with single vessel disease, 8 with two vessel disease, 19 with three vessel disease and 12 with left main stem disease), and all patients had significant narrowing of the proximal left anterior descending coronary artery or left main stem, or both.

The precordial projection of S-T segment change onto the front of the chest was used to calculate the sensitivity and specificity of electrocardiographic mapping after exercise in identifying single and three vessel disease (*Table II*). Fourteen patients (74 percent) with isolated single vessel disease had precordial projections confined to the appropriate regions of the map (sensitivity 74 percent). Ninety-three percent of patients with precordial projections of S-T segment change confined to one region of the map had isolated disease of the appropriate coronary artery (specificity

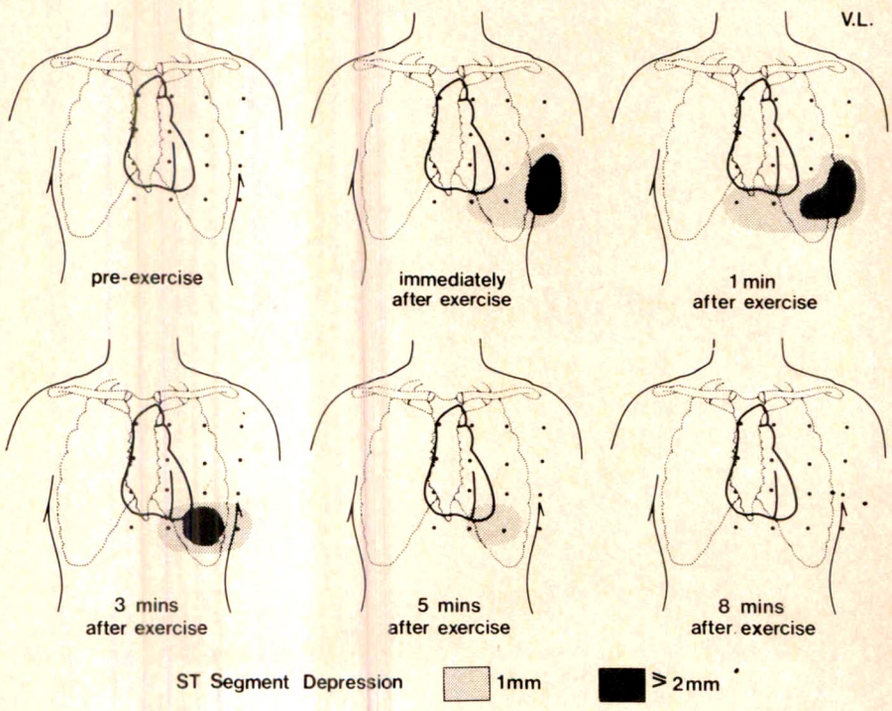

FIGURE 5. Typical sequence of contour maps of the areas of S-T segment depression in a patient with isolated right coronary artery disease. The area of S-T segment depression is localized to the inferior regions of the surface map.

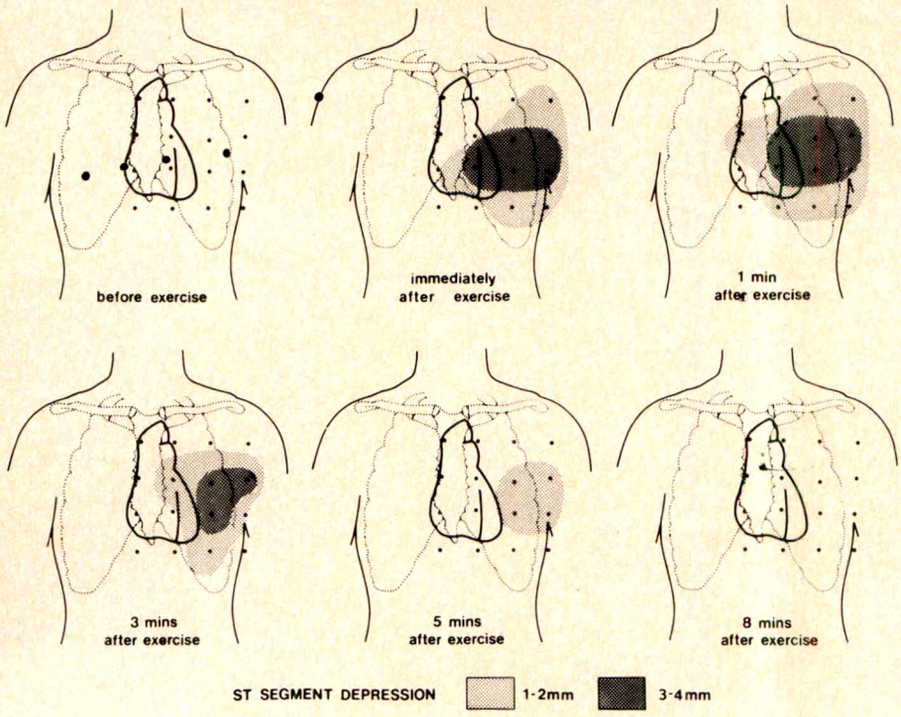

FIGURE 6. Typical sequence of contour maps of the areas of S-T segment depression in a patient with narrowing of all three coronary arteries. The S-T segment depression is seen to involve all three regions (anterior, inferior and lateral) of the map.

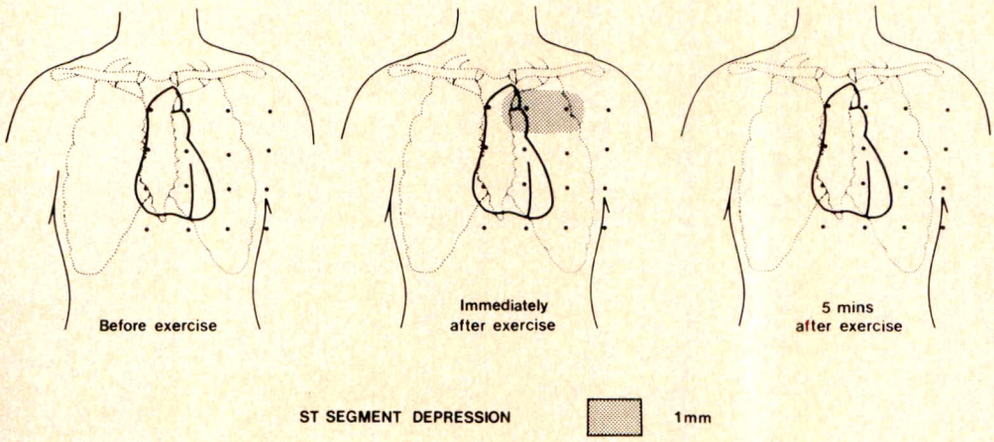

FIGURE 7. Sequence of contour maps of the area of S-T segment depression in a patient with isolated proximal left anterior descending coronary arterial narrowing. The S-T segment depression is seen to involve only the top row of the surface map. No S-T segment changes were recorded in the modified 12 lead electrocardiogram.

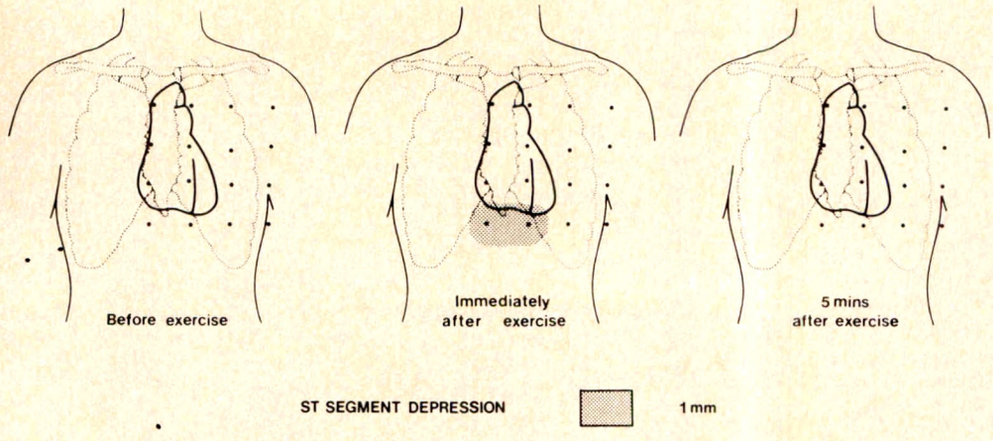

FIGURE 8. Sequence of contour maps of the area of S-T segment depression in a patient with isolated right coronary artery disease. The S-T segment depression involves only the inferior region. No S-T segment changes were recorded in the modified 12 lead electrocardiogram.

TABLE III

Sensitivity and Specificity

	Precordial Surface Mapping	Modified 12 Lead System
Sensitivity (%)	96	80
Specificity (%)	90	90

93 percent). Similarly, 21 patients (66 percent) with narrowing of all three coronary arteries had precordial projections involving all three regions (anterior, inferior, and lateral) of the surface map (sensitivity 66 percent). However, all patients with precordial projections involving all three regions of the surface map had three vessel narrowing (specificity 100 percent).

The modified 12 lead electrocardiogram: Sixty-four of the 80 patients with significant coronary arterial narrowing had S-T segment changes in the modified 12 lead electrocardiogram (sensitivity 80 percent) as did 2 of the 20 patients with normal or nonsignificant narrowing (less than 70 percent of the major coronary arteries) (specificity 90 percent).

The S-T segment changes using both the precordial and limb leads of the 12 lead electrocardiogram were used to calculate the sensitivity and specificity of this system in identifying single and three vessel disease. Isolated narrowing of the left anterior descending, right or circumflex vessel was considered present when changes were confined to the anterior (V_1 to V_5), inferior (II, III, aVf) and lateral (I, aVL, V_6) leads, respectively. Three vessel disease was considered present when S-T segment changes were found to involve all three regions. Eight patients (42 percent) with isolated single vessel disease had S-T segment changes confined to the appropriate region of the modified 12 lead electrocardiogram (sensitivity 42 percent). Ninety-three percent of patients with precordial projections confined to the anterior, inferior or lateral regions had isolated disease of the appropriate coronary artery (specificity 93 percent). Sixty-six per cent of patients with narrowing of all three coronary arteries had projections involving all three regions of the modified 12 lead electrocardiogram (sensitivity 66 percent), although all patients with S-T segment changes in all regions of the surface map had three vessel narrowing (specificity 100 percent).

Comparison between electrocardiographic mapping and the modified 12 lead electrocardiogram: Table III shows the sensitivity and specificity of the two lead systems. Precordial electrocardiographic mapping showed a significant improvement in sensitivity ($P < 0.01$) without loss of specificity ($P > 0.05$). Figure 8 shows a sequence of contour maps recorded from a patient with isolated disease of the right coronary artery. No S-T segment changes were found in this patient using the modified 12 lead electrocardiogram. Table IV lists the site of S-T segment changes and the coronary angiographic anatomy of the 13 patients correctly identified using electrocardiographic mapping

TABLE IV

Data on the 13 Patients With a Positive Exercise Map but Negative 12 Lead Exercise Test

Age (yr) & Sex	HR	Site of Precordial Ischemia	CAD
45M	160	Ant	LAD
65M	160	Ant	LAD
59F	145	Ant	LAD
46M	160	Inf	RCA
58M	150	Inf	RCA
57F	135	Ant	LAD
58M	155	Inf	RCA
51M	145	Ant	LAD
54F	120	Ant/lat	LAD/LCx
69M	125	Inf	LAD/RCA
46M	130	Ant/Lat	RCA/LCx
55M	145	Ant/lat	LMCA
49M	115	Ant/lat	LMCA

Ant = anterior; CAD = coronary artery disease (vessels with 70 percent or greater narrowing on coronary arteriography). Inf = inferior; HR = heart rate achieved (beats/min); LAD = left anterior descending coronary artery; lat = lateral; LCx = left circumflex coronary artery; LMCA = left mainstem coronary artery.

and missed using the modified 12 lead electrocardiogram. Isolated single vessel disease accounted for the majority of these patients.

Electrocardiographic mapping showed a significant improvement in sensitivity ($P < 0.01$) without significant loss of specificity ($P > 0.05$) in identifying isolated single vessel disease when compared with the modified 12 lead electrocardiogram. There was no patient in whom the modified 12 lead electrocardiogram provided a correct diagnosis that was not evident with electrocardiographic mapping. However, there was no difference between the two systems in identifying three vessel disease ($P > 0.05$). The sensitivity and specificity of the two lead systems in identifying single and three vessel disease are shown in Table V.

Discussion

Comparative sensitivity and specificity of the two systems: Precordial surface mapping was found to improve the sensitivity of exercise testing without a loss of specificity. The introduction of the 12 lead system to

TABLE V

Sensitivity and Specificity Using Electrocardiographic Mapping and Modified 12 Lead System to Identify Single and Three Vessel Disease

	Single Vessel Disease	Three Vessel Disease
Electrocardiographic mapping		
Sensitivity (%)	74	66
Specificity (%)	93	100
Modified 12 lead system		
Sensitivity (%)	42	66
Specificity (%)	93	100

exercise testing by Mason et al.[10] improved the sensitivity from approximately 60 to 80 percent.[11,12] However, there has been some doubt with regard to these figures because, as demonstrated,[13] the patient groups being studied influence the sensitivity of the technique. However, few studies, including vectorcardiographic analysis or computer analysis, have been able to show significant improvement over the 12 lead system. Any meaningful comparison between two exercise systems requires that the same groups be studied. The effects of training may also influence the results,[14] and we therefore compared the two techniques using the same patients and the same exercise test. Thus, because of the precordial lead system used, we used five chest leads covering the six positions normally occupied by the V leads of the conventional electrocardiogram. We do not believe that this compromise prejudiced our 12 lead test results because in patients with negative 12 lead tests the positive precordial S-T segment changes were distant from the conventional chest leads. Precordial surface mapping was shown to have a significantly improved sensitivity compared with the modified 12 lead system without loss of specificity. It is hoped that this improvement in diagnostic accuracy will help reduce the need for diagnostic angiocardiography.

The specificity in this study was found to be very high using both lead systems. This is almost certainly due to the sample of patients studied. There were very few young women studied, a group characteristically known to have a large incidence of false positive tests.[15]

Correlations with site and severity of coronary artery disease: In this study the relation between the precordial projection of S-T segment changes and the coronary angiographic anatomy was investigated and a comparison made with the findings using a modified 12 lead electrocardiogram. Correlation between S-T segment changes and the site of coronary arterial stenosis is poor using the simpler lead systems. Demany et al.[16] and McHenry et al.[17] were unable to find a positive correlation using a limited number of leads. The introduction of the 12 lead exercise electrocardiogram to exercise testing has provided some information, particularly in single vessel disease.[18] The use of the electrocardiographic mapping technique in exercise testing provides an extra dimension to the stress test because it allows a measurement to be made of the area of precordial S-T segment changes. It is therefore necessary to determine whether any relation exists between these precordial S-T segment changes and the coronary arterial anatomy.

In this study patients with three vessel disease manifested larger areas of precordial electrocardiographic change than those with only one or two vessel involvement as did patients with two vessel disease compared with those with single vessel disease. In addition, the severity of precordial S-T segment changes (total S-T segment depression in millimeters) revealed a similar relation to the coronary arterial anatomy. However, although statistically significant, the wide overlap in the area and severity of S-T segment changes of patients with one, two and three vessel disease makes it difficult to formulate any firm conclusions in an individual patient in terms of assessing the extent of coronary artery disease using these two electrocardiographic variables alone.

Correlations of site of S-T changes and coronary artery disease: The use of the site of S-T segment changes projected onto the precordium was found to be more valuable than the area or severity of S-T changes. Theoretically there are several factors that severely limit any interpretation of the coronary arterial anatomy from the precordial projection of S-T segment changes. Variable embryologic development in man means that an ischemic segment of myocardium can be supplied by any one or two of the three major coronary arteries. In addition, the location and distribution of the precordial electrocardiographic changes depend on the site of the ischemic area and the position of the heart in relation to the 16 positions on the chest, the distance between the electrodes and the heart and the resistance of the tissues between.[19] The borders of the electrocardiographic manifestations are influenced by the adjacent normal tissue. Further, the presence or absence of collateral circulation and the possible effects of "coronary steal" also affect the precordial projection of S-T segment changes.[18]

Accepting these reservations, we found a typical precordial projection in 74 percent of patients with single vessel disease and disease of the appropriate coronary artery in 93 percent of patients with a typical projection. These findings were a significant improvement over those obtained with the modified 12 lead electrocardiogram when a direct comparison was made. In addition, the projection of S-T segment changes high in the surface map proved to be a highly specific finding in patients with left main stem or proximal narrowing of the left anterior descending coronary artery. This information was not obtained from the 12 lead electrocardiogram and may be important in the management of patients presenting with chest pain. Patients with S-T segment changes involving all the regions of the precordium (anterior, inferior and lateral) were found to have disease in all three coronary arteries. However, this information was also available from the modified 12 lead electrocardiogram.

All the patients in this study gave a history of chest pain. It is well known that the sensitivity and specificity of exercise testing are always better when the patients studied have typical angina pectoris.[13] However, it is specifically in this group of patients that any noninvasive information obtained about the coronary arterial anatomy is most valuable.

Implications: Our study has shown that electrocardiographic mapping provides additional information regarding the coronary arterial anatomy not available using the conventional 12 lead electrocardiogram. Further studies are necessary to confirm the role of this technique in routine noninvasive evaluation of patients presenting with chest pain, although the results appear to be promising.

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Hemodynamic Response to Exercise After Propranolol in Patients With Mitral Stenosis

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Hemodynamic response to exercise before and 10 minutes after propranolol (5 mg intravenously) was studied in 10 young patients with pure mitral stenosis who had normal sinus rhythm and no cardiac failure. After propranolol the mean heart rate and cardiac index at rest were lower than during the control state (respectively, 95 ± 4 versus 82 ± 3 beats/min, $P < 0.005$; 3.4 ± 0.2 versus 2.8 ± 0.1 liters/min per m^2, $P < 0.025$). As a result, the mean pulmonary wedge pressure and mean mitral valve gradient at rest were lower (respectively, 22 ± 2 versus 18 ± 2 mm Hg, $P < 0.005$; 24 ± 2 versus 17 ± 2 mm Hg, $P < 0.001$). During exercise after propranolol the values of pulmonary wedge pressure and mitral valve gradient were lower than control values during exercise (respectively, 39 ± 3 versus 30 ± 2 mm Hg, $P < 0.005$; 44 ± 3 versus 32 ± 3 mm Hg, $P < 0.005$), again because of the lower heart rate and cardiac index (130 ± 6 versus 104 ± 6 beats/min, $P < 0.001$; 4.6 ± 3 versus 3.7 ± 2 liters/min per m^2, $P < 0.01$). Left ventricular end-diastolic pressure and stroke index showed no significant changes. Thus, propranolol may benefit patients with pure mitral stenosis with sinus rhythm and no cardiac failure whose symptoms occur during those reversible conditions characterized by an increase in heart rate or cardiac output, or both.

In patients with pure mitral stenosis the symptoms are usually due more to pulmonary venous hypertension than to low cardiac output or right ventricular failure. For any given valve area, the pulmonary venous pressure is an inverted exponential function of the heart rate and the cardiac output.[1] If the mitral valve area formula is solved for the diastolic mitral valve pressure gradient, and if the valve area, which does not vary acutely, is incorporated in a constant (K), the pressure gradient across the stenotic mitral valve can be obtained as follows:

$$\text{Mitral valve pressure gradient} = \left(\frac{\text{Cardiac output}}{\text{K} \times \text{Diastolic filling period}}\right)^2.$$

Thus an increase in cardiac output or a decrease in diastolic filling period results in an exponential rise in valve pressure gradient. Because the diastolic filling period is shortened as the heart rate increases, this equation explains the appearance of symptoms in patients with mitral stenosis when heart rate or cardiac output, or both, is increased.

Beta adrenergic blocking agents reduce the diastolic pressure gradient across the stenotic mitral valve, and thus pulmonary congestion, by decreasing both heart rate and cardiac output.[2–7] However, it has been suggested[8–12] that the negative inotropic effects of propranolol, by depressing cardiac performance and thus increasing left ventricular end-diastolic pressure, may counteract these beneficial effects.

Various hypotheses have been suggested regarding the effects of propranolol in patients with mitral stenosis and atrial fibrillation. Some investigators[8,13] consider the drug effective in reducing heart rate both during rest and after exercise; other investigators[14] maintain that pro-

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pranolol is more effective in limiting chronotropic response to exercise in patients with sinus rhythm than in those with atrial fibrillation. This was not investigated in this study. The object of our investigation was to evaluate the hemodynamic response to exercise after propranolol in patients with pure mitral stenosis, sinus rhythm and no cardiac failure.

Methods

Study patients: Ten patients, aged 25 to 37 years, with pure mitral stenosis, sinus rhythm and no cardiac failure, were selected from a wide range of patients with valve disease examined from February 1975 to December 1977 and studied during cardiac catheterization performed to evaluate their need for cardiac surgery. Every drug was suspended for at least 7 days before the hemodynamic investigation. No history of angina was present in any patient and no aortic valve disease or mitral regurgitation was documented during cardiac catheterization.

Three patients (Cases 3, 6 and 10) (Table I) were considered to be in New York Heart Association[15] functional class I, two in class II (Cases 8 and 9) and five in class III. Clinical and hemodynamic data are reported in Table I.

Cardiac catheterization procedures: Right and left heart catheterization was performed in every patient through the right brachial vein and artery. A no. 7F Cournand catheter was placed in the pulmonary wedge position and maintained in this position throughout the period of investigation. A no. 7F Swan-Ganz Edwards catheter for thermodilution was introduced through a superficial right arm vein and placed into the main pulmonary artery. Cardiac output was obtained with the thermodilution technique using an Edwards Cardiac Output Computer 9500, and pressure measurements were obtained using Statham P23Db pressure transducers. All data were recorded on an OTE Biomedica preamplifier. The Swan-Ganz catheter was withdrawn in the right ventricle at various stages of the investigation to measure the first derivative of right ventricular pressure (dP/dt max). A no. 8F Lehman catheter was introduced into the left ventricle for pressure measurements and, at the end of the investigation, it was utilized for left ventriculography, which excluded the presence of mitral regurgitation. Aortic angiography excluded the presence of aortic valve disease.

TABLE I

Hemodynamic Measurements in 10 Patients

	HR	CI	SI	LVSP	LVEDP	dP/dt max LV	dP/dt max RV	PAP	PWP	MVG	PVRI
Case 1 (25 years, female, MVA = 1.1 cm²)											
A	70	3.1	44	137	5	1346	1001	53	25	25	303
B	160	3.5	22	176	8	2243	2304	80	40	48	379
C	115	3.0	26	144	6	1601	1582	55	34	34	230
D	100	2.8	28	128	8	1221	1280	54	30	27	285
E	130	2.8	22	137	12	1609	1608	70	38	34	374
Case 2 (31 years, female, MVA = 1.8 cm²)											
A	103	3.3	31	142	6	2586	475	34	31	25	32
B	150	4.3	28	195	4	5106	871	55	53	56	17
C	103	3.2	30	131	9	2389	601	26	24	20	22
D	85	2.9	33	136	6	1833	528	24	17	16	86
E	115	3.8	32	135	8	2422	709	47	38	33	85
Case 3 (25 years, female, MVA = 1.7 cm²)											
A	70	3.9	55	102	10	1484	368	22	20	15	16
B	105	6.6	62	117	7	1856	432	38	29	33	42
C	75	3.6	48	100	10	1392	336	24	18	19	52
D	68	3.0	44	106	8	1207	448	21	14	14	73
E	75	3.8	50	104	8	1388	416	34	22	22	99
Case 4 (37 years, female, MVA = 0.7 cm²)											
A	80	2.7	34	122	14	2220	359	33	31	28	25
B	150	3.6	24	157	11	3861	412	47	44	38	29
C	105	2.8	27	138	12	2220	362	27	25	28	25
D	75	2.3	30	116	16	1834	287	23	20	17	46
E	98	2.5	25	130	11	2316	466	33	30	20	42
Case 5 (32 years, female, MVA = 0.8 cm²)											
A	80	3.1	38	118	10	2008	260	31	15	25	219
B	125	3.9	31	148	11	3199	295	71	33	—	411
C	100	3.0	30	120	10	2504	191	45	23	—	307
D	83	2.6	31	125	13	2602	130	39	17	—	354
E	87	3.2	37	125	11	2900	243	67	25	—	545

Continued

TABLE I (Continued)

	HR	CI	SI	LVSP	LVEDP	dP/dt max LV	dP/dt max RV	PAP	PWP	MVG	PVRI
Case 6 (30 years, female, MVA = 2.1 cm^2)											
A	110	4.1	36	140	7	2232	280	14	12	10	14
B	140	5.3	37	160	5	3497	446	22	21	—	6
C	110	4.2	38	135	6	2230	283	16	11	—	34
D	90	2.8	31	133	12	1785	178	14	12	—	20
E	120	5.0	41	142	7	2320	461	29	24	—	29
Case 7 (20 years, female, MVA = 1.4 cm^2)											
A	66	3.2	47	112	16	1602	347	28	24	8	31
B	107	4.0	37	145	17	3038	763	52	43	45	54
C	79	3.0	37	122	12	1909	434	25	20	19	41
D	84	3.3	39	125	20	1822	459	24	13	10	81
E	106	4.2	39	138	17	2690	595	35	25	36	58
Case 8 (26 years, female, MVA = 0.8 cm^2)											
A	75	2.2	30	122	6	1224	595	35	25	20	148
B	118	4.4	38	105	8	1400	692	68	43	—	187
C	75	3.1	41	126	8	962	518	37	25	—	127
D	68	3.0	44	124	6	888	444	35	22	—	143
E	85	3.7	44	130	8	1036	520	49	33	—	143
Case 9 (35 years, male, MVA = 1.4 cm^2)											
A	90	4.2	46	105	7	2065	286	38	25	22	73
B	118	6.0	50	115	10	2408	852	68	50	44	70
C	90	4.2	47	110	8	2309	379	37	22	25	82
D	80	3.3	41	110	9	1548	254	35	20	20	105
E	100	4.1	40	103	9	1413	665	60	35	40	144
Case 10 (36 years, male, MVA = 1.5 cm^2)											
A	85	2.9	34	110	9	1696	250	32	22	25	86
B	130	4.2	32	120	10	2098	432	50	32	43	105
C	95	3.3	28	105	8	1540	260	28	22	25	44
D	90	2.1	23	97	9	1249	200	20	16	14	48
E	120	3.6	30	105	12	1607	486	41	29	38	81

A = control hemodynamic measurements; B = measurements during control exercise period (50 watts/min per 10 minutes); C = recovery measurements; CI = cardiac index (liters/min per m^2); D = measurements 10 minutes after injection of propranolol; dP/dt max LV = first derivative of left ventricular pressure (mm Hg/sec); dP/dt max RV = first derivative of right ventricular pressure (mm Hg/sec); E = exercise after propranolol; HR = heart rate (beats/min); LVEDP = left ventricular end-diastolic pressure (mm Hg); LVSP = left ventricular systolic pressure (mm Hg); MVA = mitral valve area; MVG = mean diastolic transmitral pressure gradient (mm Hg); PAP = mean pulmonary arterial pressure (mm Hg); PVRI = pulmonary vascular resistance index (dynes sec cm^{-5}/m^2); PWP = mean pulmonary wedge pressure (mm Hg); SI = stroke index (ml/beat per m^2).

Exercise and propranolol protocol: After the control data were recorded, exercise in the supine position was carried out at 50 watts/min with an electronically braked leg ergometer and maintained for 10 minutes. Exercise measurements were recorded from the 7th minute. Recovery measurements were obtained 20 minutes after the interruption of the exercise or when pulmonary pressure and cardiac output were similar to the control data. Five mg of propranolol was administered as a single bolus injection into the pulmonary artery. All data were recorded 10 minutes after the injection of propranolol and again during the same work load. Mean diastolic mitral valve pressure gradient was calculated using the three points method.[16] Mitral valve areas were calculated according to the Gorlin formula.[17,18] The values observed during the control exercise period were compared with the control data; the values recorded during the second exercise period were compared with the values obtained after the injection of propranolol; the values observed after propranolol injection were compared with the measurements made during recovery.

Statistical analyses: The results of this study are expressed as mean ± standard error. Analyses were performed using the Student's t test method[19] with each patient serving as his own control.

Results

The results of all the hemodynamic measurements are reported in Tables I to IV and some are shown graphically in Figures 1 and 2.

Heart rate increased from 83 ± 4 to 130 ± 6 beats/min ($P < 0.001$) during the control exercise period; after propranolol it decreased from 95 ± 4 to 82 ± 3 beats/min ($P < 0.005$). During exercise after beta adrenergic

TABLE II

Mean Values ± Standard Error and Statistical Significance of Hemodynamic Measurements in 10 Patients

	A		B	C		D		E
HR	83 ± 4	$P<0.001$	130 ± 6	95 ± 4	$P<0.005$	82 ± 3	$P<0.001$	104 ± 6
CI	3.3 ± 0.2	$P<0.001$	4.6 ± 0.3	3.4 ± 0.2	$P<0.025$	2.8 ± 0.1	$P<0.005$	3.7 ± 0.2
SI	39 ± 2	NS	36 ± 4	35 ± 2	NS	34 ± 2	NS	36 ± 3
LVSP	121 ± 4	$P<0.01$	143 ± 9	123 ± 5	NS	120 ± 4	NS	125 ± 5
LVEDP	9 ± 1	NS	9 ± 1	9 ± 1	NS	11 ± 1	NS	10 ± 1
dP/dt max LV	1,846 ± 140	$P<0.005$	2,871 ± 348	1,906 ± 161	$P<0.005$	1,599 ± 154	$P<0.005$	1,970 ± 200
dP/dt max RV	422 ± 73	$P<0.05$	750 ± 184	495 ± 127	NS	421 ± 105	$P<0.005$	617 ± 117
PAP	32 ± 3	$P<0.001$	55 ± 5	32 ± 4	$P<0.005$	29 ± 4	$P<0.001$	46 ± 5
PWP	23 ± 2	$P<0.001$	39 ± 3	22 ± 2	$P<0.005$	18 ± 2	$P<0.001$	30 ± 2
MVG	21 ± 3	$P<0.001$	44 ± 3	24 ± 2	$P<0.001$	17 ± 2	$P<0.01$	32 ± 3
PVRI	95 ± 31	NS	130 ± 47	96 ± 31	$P<0.01$	124 ±35	NS	160 ± 53

Abbreviations as in Table I. NS = not significant.

blockade, both the absolute value and the increment of heart rate were lower than the values during the control exercise period (Fig. 1 and 2 and Tables III and IV).

Cardiac index increased from 3.3 ± 0.2 to 4.6 ± 0.3 liters/min per m^2 ($P<0.001$) during the control exercise period. After propranolol, it decreased from 3.4 ± 0.2 to 2.8 ± 0.1 liters/min per m^2 ($P<0.025$) at rest and then increased to 3.7 ± 0.2 liters/min per m^2 ($P<0.005$) during exercise, so that the values during exercise after propranolol were significantly lower than the values during the control exercise period (Fig. 1 and Table III). *Stroke index* remained essentially unchanged, suggesting that the variations in cardiac output were strictly related to the modifications in heart rate.

Pulmonary wedge pressure increased from 23 ± 2 to 39 ± 3 mm Hg ($P<0.001$) during the control exercise period. After propranolol it decreased from 22 ± 2 to 18 ± 2 mm Hg ($P<0.005$) during rest, and then increased to 30 ± 2 mm Hg ($P<0.001$) during exercise.

Mitral valve pressure gradient revealed the same patterns as pulmonary wedge pressure (Fig. 1 and 2, Tables I to IV). During exercise after propranolol both the latter measurements reached values significantly lower than those reached during the control exercise period (Table III).

Left ventricular end-diastolic pressure showed no significant modifications (Fig. 1, Table II).

Left ventricular systolic pressure significantly increased during the control exercise period. After propranolol, no significant change was noted, either at rest or during exercise. Thus, propranolol considerably blunted the increase in arterial pressure during exercise (Tables II to IV).

TABLE III

Mean Values ± Standard Error and Statistical Significance of the Various Measurements During Exercise Carried Out Before and After Propranolol

	Before	After	*P* Value
HR	130 ± 6	104 ± 6	<0.001
CI	4.6 ± 0.3	3.7 ± 0.2	<0.01
SI	36 ± 4	36 ± 3	NS
LVSP	143 ± 9	125 ± 5	<0.05
LVEDP	9 ± 1	10 ± 1	NS
dP/dt max LV	2,871 ± 348	1,970 ± 200	<0.01
dP/dt max RV	750 ± 184	617 ± 117	NS
PAP	55 ± 5	46 ± 5	<0.01
PWP	39 ± 3	30 ± 2	<0.005
MVG	44 ± 3	32 ± 3	<0.005
PVRI	130 ± 47	160 ± 53	NS

NS = not significant; *P* = probability; other abbreviations as in Table I.

TABLE IV

Statistical Comparison of the Mean Increases in Hemodynamic Values Observed During Control Exercise and Exercise After Propranolol

	Control Exercise	Exercise After Propranolol	*P* Value
HR	47 ± 6	22 ± 3	<0.01
CI	1.3 ± 0.2	0.9 ± 0.2	NS
SI	−3 ± 3	2 ± 2	NS
LVSP	22 ± 6	5 ± 2	<0.05
LVEDP	0 ± 1	−1 ± 1	NS
dP/dt max	1,025 ± 233	371 ± 87	<0.01
dP/dt max RV	328 ± 122	196 ± 42	NS
PAP	23 ± 3	17 ± 2	NS
PWP	16 ± 2	12 ± 1	<0.05
MVG	23 ± 3	15 ± 3	<0.001
PVRI	35 ± 19	36 ± 20	NS

NS = not significant; *P* = probability; other abbreviations as in Table I.

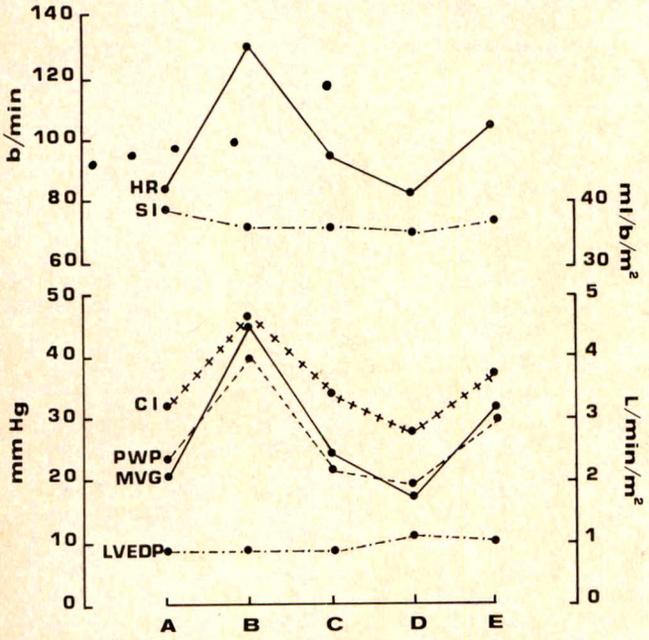

FIGURE 1. Mean values of some hemodynamic measurements observed during the various phases of the study. Cardiac index (CI, liters[L]/min per m^2), heart rate (HR, beats [b]/min), transmitral gradient (MVG, mm Hg) and mean pulmonary wedge pressure (PWP, mm Hg) change in the same direction. Left ventricular end-diastolic pressure (LVEDP, mm Hg) and stroke index (SI, ml/beat per m^2) do not vary. A = control measurements at rest; B = measurements during control period of exercise (50 watts/min per 10 minutes); C = recovery measurements; D = measurements 10 minutes after injection of propranolol; E = measurements during exercise after propranolol.

Discussion

In patients with mitral stenosis the increase in heart rate or cardiac output, or both, leads to an increase of pulmonary venous pressure that determines the appearance of dyspnea and of pulmonary congestion. Digitalis does not benefit these patients because it reduces heart rate only slightly during sinus rhythm and has no effect on cardiac output in the absence of cardiac failure.[20] Diuretic drugs should reduce pulmonary venous pressure by decreasing cardiac output alone because the heart rate is not modified.[21] Another explanation may be that diuretic drugs decrease blood volume and the filling (diastolic) pressure on both sides of the heart drops a few mm Hg.

Effect of propranolol on exercise hemodynamics in mitral stenosis: Beta adrenergic blocking drugs like propranolol decrease pulmonary venous pressure and mitral valve gradient at rest by reducing heart rate and cardiac output. Moreover, during exercise, these drugs specifically and selectively inhibit the effects of increased heart rate and cardiac output and blunt the rise in arterial pressure.[22–27] Therefore, light exercise after propranolol is accomplished at a slower heart rate and a slightly lower cardiac output. Similar changes occurred in our patients with mitral stenosis so that after propranolol their heart rate and cardiac index at rest were lower than during the control state. As a result the resting pulmonary wedge pressure and mitral valve gradient were lower. Moreover, during exercise after propranolol pulmonary wedge pressure and mitral valve

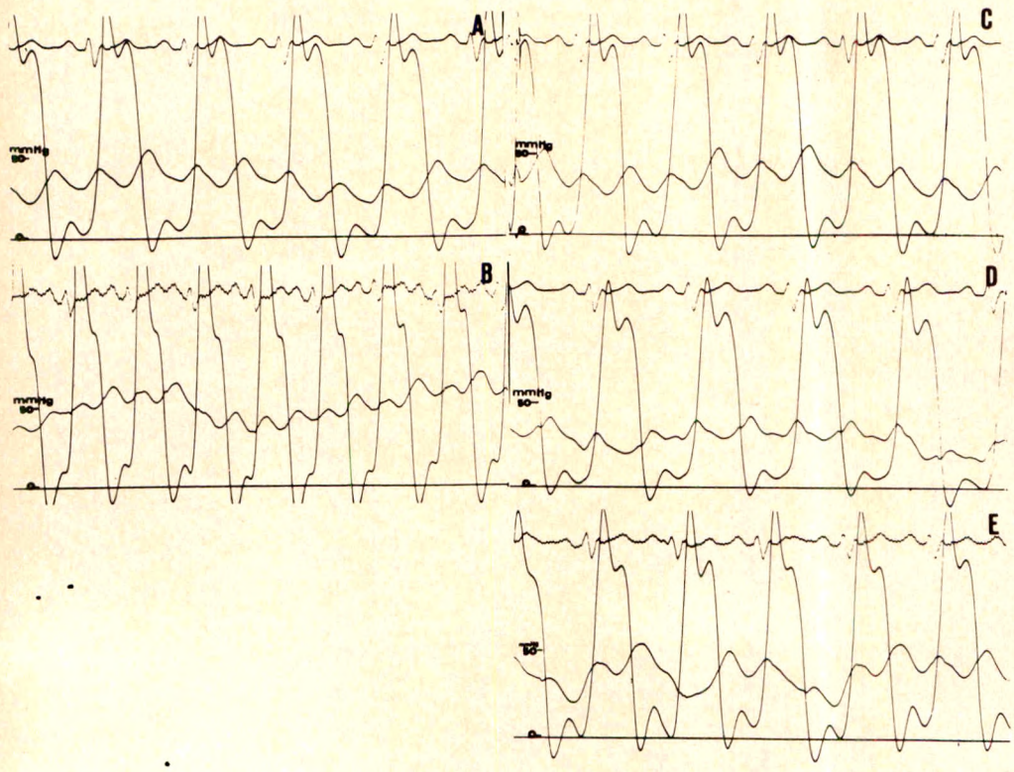

FIGURE 2. Simultaneous, equisensitive left ventricular and pulmonary wedge pressures in a representative patient. The values for heart rate and mitral valve gradient during exercise after propranolol (E) are less than during the control exercise period (B). Propranolol (D) clearly decreases heart rate and mitral valve gradient. (Paper speed = 100 mm/sec.) Tracings from **top down** in each panel are electrocardiogram, pulmonary wedge pressure and left ventricular pressure. A, B, C, D and E as in Figure 1.

gradient were lower than during the control exercise period, again because of the lower heart rate and cardiac index.

It is known[22–27] that light exercise in the supine position at a work load of about 50 watts/min increases cardiac output primarily by an increase in heart rate with little or no change in stroke volume. After a period of rest, the cardiac output returns to control levels but heart rate usually remains higher than during the first control period. This occurred in 6 of our 10 patients. As a result the mean value of heart rate during rest before propranolol was greater than during the original resting control period, and four patients had a faster heart rate during rest after propranolol than during the resting control period. Nevertheless, the absolute values of heart rate during exercise after propranolol, at the same work load, were lower than during control exercise, because of the marked inhibition of the tachycardia by propranolol during exercise.

Effect of propranolol on dyspnea and fatigue during exercise: During the control exercise period all patients experienced mild or severe dyspnea. During exercise after propranolol only two patients (Cases 1 and 2) had slight dyspnea, whereas all patients had trouble in carrying out the same work load, because the leg fatigue was more severe than during control exercise. It is known[22–27] that subjects performing supine exercise at a mild (50 watts) to moderate (100 watts) work load using a leg ergometer tend to note as the first sign of fatigue "tiredness" in the limbs rather than shortness of breath. When they are given a beta adrenergic blocking drug this leg fatigue appears earlier and is more severe at any given load, probably because the distribution of cardiac output is not as effectively shunted to the legs and away from other vascular beds and nonexercising muscle beds.

Effect on pulmonary congestion and wedge pressure: Because pulmonary congestion is responsible for the symptoms observed in patients with mitral stenosis, a moderate reduction in cardiac output seems acceptable in exchange for a decreased pulmonary venous pressure. The reduction in cardiac output may be strictly related to the decreased heart rate because the stroke volume remains essentially unchanged. Thus, the decrease in heart rate is the main factor that produces the decrease in pulmonary wedge pressure and mitral valve gradient, because left ventricular end-diastolic pressure did not change. This finding is in accordance with the data of Bhathia et al.,[2] who reported that pulmonary wedge pressure did not change after propranolol in patients whose heart was paced with an external fixed rate pacemaker. Immediately after pacing, wedge pressure clearly decreased; this was related to the extension of the diastolic filling period, because the stroke volume did not vary.

Implications: Inhibition of the tachycardia by propranolol during exercise seems to benefit greatly patients with mitral stenosis. Beta adrenergic blocking agents may be "protective" in patients with pure mitral stenosis, sinus rhythm and no cardiac failure whose symptoms occur during those reversible conditions (exercise, pregnancy, hyperthyroidism, fever and anemia, for example) characterized by an increase in heart rate or cardiac output, or both.

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Histopathologic Correlates of Left Posterior Fascicular Block

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Thirteen hearts from subjects (10 male, 3 female; mean age 65 years) with left posterior fascicular block were studied. Left posterior fascicular block was associated with right bundle branch block in nine cases and alternated with left anterior fascicular block in three. In nine of the patients, the conduction disorders were observed during an episode of acute myocardial infarction. Of these nine patients, four showed interruptive lesions at the level of the posterior radiation of the left bundle or of the posterior portion of the main left bundle branch. Two were found to have severe alterations scattered throughout the left bundle branch system: One of them had alternating left anterior and left posterior fascicular block; and the other manifested complete heart block in the course of her illness. No interruptive changes of the posterior fibers were found in three cases in which the heart was obtained early after death. All 9 patients had severe coronary artery disease (six had triple vessel disease and three of the six had a left main coronary arterial stenosis or obstruction; two patients had double vessel disease). Among the four patients with chronic left posterior block, three were found to have heavy calcifications of the left side of the cardiac skeleton; the remaining one had diphtheritic myocarditis. All had major alterations of the left-sided conduction system that were consistently maximal at the level of the posterior fibers or posterior portion of the main left bundle branch. In two of these patients scattered lesions were found throughout the left bundle branch fibers; one had alternating left anterior and left posterior fascicular block and the other had complete heart block. In general, the alterations underlying left posterior fascicular block were less widely spread than in left anterior fascicular block; however, they were more severe and more proximally located.

In 1972, we[1] reported our histologic findings in hearts from patients with left anterior fascicular block. Left posterior hemiblock is rarer and much more difficult to identify with certainty, and we therefore needed additional time to collect a similar series of left posterior fascicular block for histologic analysis. In this report we describe our pathologic observations in 13 cases of left posterior fascicular block, including 4 chronic cases and 9 that had appeared during an acute myocardial infarction.

Methods

Case material: Thirteen hearts from subjects (10 male, 3 female) aged 28 to 85 years (mean 65 years) with left posterior fascicular block were studied. The following criteria were used for recognition of isolated left posterior fascicular block[2]: (1) total QRS duration shorter than 120 msec; (2) deviation of QRS axis in the frontal plane to the right of +120°; and (3) ventricular complexes showing an rS configuration in leads I and aVL and a qR pattern in leads II, III and aVF

The following criteria were utilized for the diagnosis of combined right bundle branch block and left posterior fascicular block: (1) QRS duration of 0.12 second or longer; (2) terminal R or R′ wave in lead V_1; (3) mean frontal QRS axis at +120° or further; and (4) presence of a deep S wave in leads I and aVL and of a tall R wave in leads II, III and aVF.

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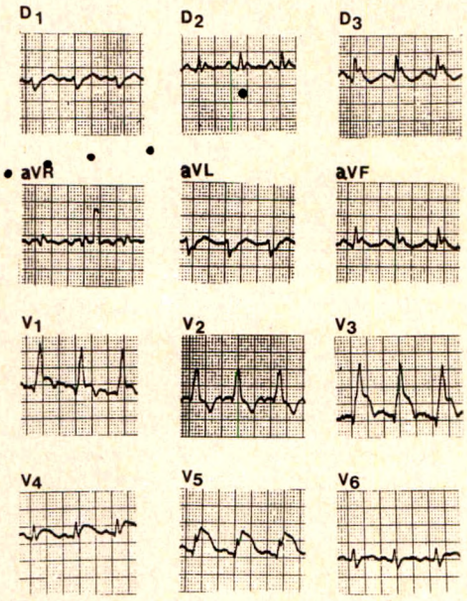

FIGURE 1. Case 2. Patient with a history of old inferior myocardial infarction who manifested left posterior fascicular block with right bundle branch block during the course of an acute anterior infarction.

Three observers examined the clinical file and the serial electrocardiograms of each patient to make sure that the right axis deviation was due to no cause other than the conduction disorder. In addition, we excluded all patients whose heart showed right ventricular hypertrophy at autopsy (right ventricular wall thickness 4 mm or more). Figures 1 and 2 show the electrocardiographic tracings in two cases.

The relevant clinical and anatomic data are summarized in Table I. In nine cases, the conduction disturbance developed during the course of an acute myocardial infarction. In the remaining four cases left posterior fascicular block had been present for at least 1 year before death. Left posterior fascicular block was associated with right bundle branch block in nine persons; in three of them, it alternated with left anterior fascicular block (constant right ventricular conduction delay constantly associated with a pattern of fascicular block).

Pathologic examination: All hearts were studied by serial sectioning of the septum. For serial sectioning, the plane of cutting was according to the recommendations of Mahaim[3] (parallel to the atrioventricular [A-V] ring) in two cases and according to those of Lev and McMillan[4] (perpendicular to the A-V ring) in the others. Slices 6 μ thick were prepared. Every 40th section was routinely stained with hematoxylin-eosin and studied. Whenever examination of initially selected samples suggested it would be useful, intervening sections were later stained and viewed. The left bundle branch and its subdivisions were identified by their subendocardial location and by the various differentiating histologic features characteristic of the conduction system.

In the four cases in which left posterior fascicular block was not observed in the setting of a myocardial infarction, a stereologic quantification of fibrosis was performed.[5,6] For this purpose, a section was retained every 2 mm. The microscope was fitted with a projection head that permitted projection of the image to be studied on a ground glass screen. A Weibel's point test system[5] was superimposed on these images. The number of points falling on fibrotic tissue (Pf) and the number of points falling on specific muscle fibers (Pm) were determined. These measurements allowed calculation of the relative volumetric density of fibrosis (Vv):

$$Vv = Pf/(Pf + Pm)$$

By combining the topographic reconstruction of the left bundle branch system with the stereologic data, it was possible to map the geometry of the left bundle branch ramifications and to indicate at each level the corresponding density of fi-

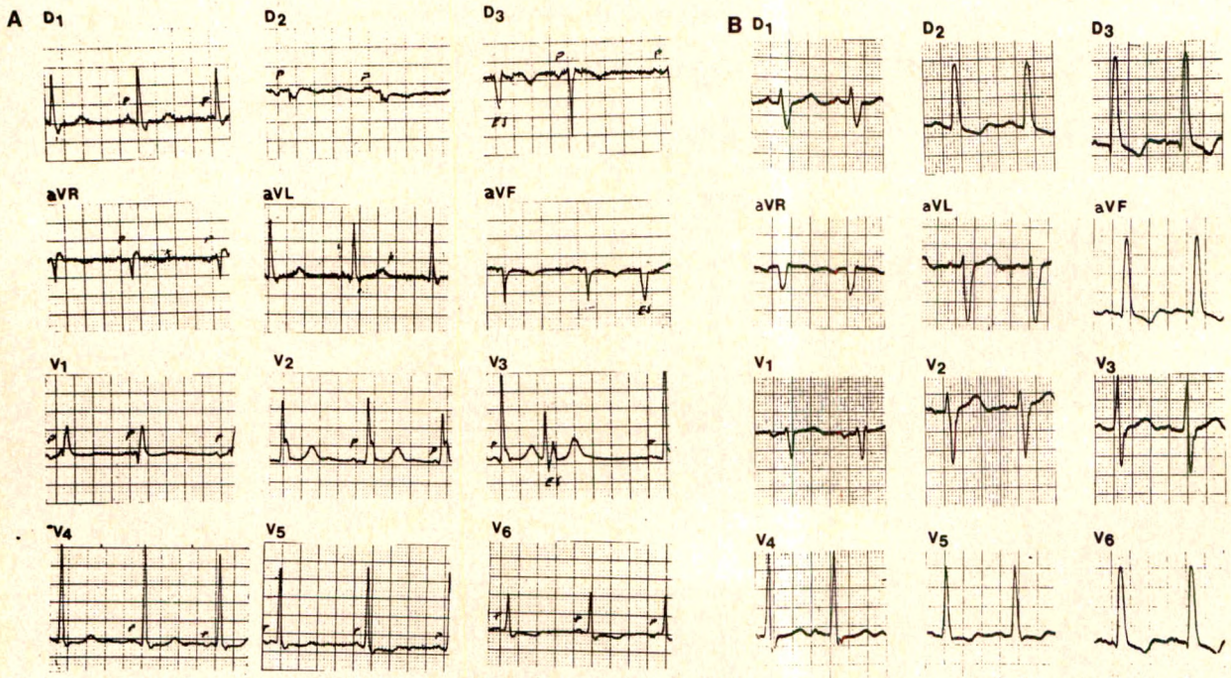

FIGURE 2. Case 12. Electrocardiograms of a patient who had alternating **(A)** left anterior fascicular block with complete right bundle branch block and **(B)** left posterior fascicular block with incomplete right bundle branch block morphology in lead V_1.

brosis. Details regarding this technique and the treatment of the data that it provides have previously been described.[6]

Results

The cases were classified according to the presence or absence of acute myocardial infarction.

Patients with acute myocardial infarction: In this subgroup, the coronary arterial lesions were severe. Among the nine patients, six had triple and two had double vessel disease. Three patients had a subtotally or totally obstructed left main coronary artery. Figure 3 illustrates the location of the histopathologic lesions observed in these nine hearts. In Cases 1 and 2, there were simultaneous acute and chronic changes that interrupted the posterior portion of the main left bundle and the proximal part of the posterior radiation. Only scattered areas of fibrosis were evident in Case 3; this heart had been obtained very early after the onset of symptoms and no acute lesions were found along the posterior fibers. In two cases (Cases 4 and 8), severe alterations were found along both the anterior and posterior ramifications. In one of these cases left anterior and left posterior fascicular block alternated; in the other, complete heart block developed during the course of the infarction. In Cases 5 and 7 some areas of fibrosis or inflammatory infiltration were observed, but no interruptive lesion was disclosed at the level of the posterior fascicle. Finally, in Cases 6 and 9, the histopathologic alterations were specifically located at the level of the posterior radiation.

In some patients, associated chronic or acute lesions were seen to lie within the A-V node (four cases) or common His bundle (five cases), or to interrupt the right bundle branch (five cases).

Patients without myocardial infarction: Two of the four patients with chronic left posterior fascicular block without acute myocardial infarction had no coronary arterial lesion. Of the remaining two, one had an obstructed circumflex artery and the other had double vessel disease. Figure 4 presents diagrams of the left bundle branch system in the hearts of the four cases. The value of the relative density of fibrosis is indicated at all levels where it was measured. In all four cases, fibrotic and degenerative changes were seen in the left-sided conduction system. In two cases more acute alterations (inflammatory infiltration) were evident. The lesions were consistently maximal at the level of the posterior fibers of the left branch and of the posterior part of the main left bundle. However in two other cases (Cases 12 and 13), the lesions were scattered throughout the left bundle branch system, and acute changes (Case 12) or severe fibrosis was also found along the anterior subdivision. In those two cases there was electrocardiographic evidence of diffuse involvement of the left

TABLE I

Clinical and Anatomic Findings

Case no.	Age (yr) & Sex	Diagnosis	Electrocardiogram	Anatomic Findings: Coronary Arteries LCA	LAD	LCx	RCA	Calcifications
			A. Patients With Left Posterior Fascicular Block and Acute Myocardial Infarction					
1	73M	Old anterior MI; acute inferior MI	RBBB + LPFB; 2° A-V block	N	St	N	St	+++
2	70M	Old inferior MI; acute anterior MI	RBBB + LPFB	Ob	N	N	St	+
3	64M	Recent inferior MI	RBBB + LPFB	St	N	N	Ob	0
4	73M	Recent anterior MI	RBBB + LPFB or LAFB alternatively	Ob	N	N	St	++
5	85M	Recent inferior MI + cerebrovascular accident	Intermittent RBBB + LPFB	N	N	Ob	St	++
6	58F	Diabetes mellitus; subendocardial inferior MI	LPFB	N	St	St	Ob	0
7	56M	Small anterior scar: Prinzmetal's angina; ventricular fibrillation	Alternating LAFB or LPFB + RBBB (during angina)	N	Ob	Ob	St	0
8	65F	Old and recent inferior MI	RBBB + LPFB, 3° A-V block, LPFB	N	N	N	Ob	0
9	63M	Unstable angina; old anterior and inferolateral MI; recent MI		N	St	Ob	Ob	0
			B. Patients With Chronic Left Posterior Fascicular Block					
10	75M	Small ASD; sarcoidosis; GI bleeding	LPFB	N	N	N	N	+++
11	28M	Diphtheritic myocarditis	Sinoatrial disease, RBBB + LPFB, 3° A-V block	N	N	N	N	0
12	65M	Old posterior scar; Stokes-Adams attacks	RBBB + LAFB or alternating with severe LPFB + incomplete RBBB, LPFB	N	N	Ob	N	+++
13	73M	Alcoholism; infected burns and septicemia		0	St	St	N	+++

Calcifications of the upper intraventricular septum, valve rings and central fibrous body: 0 = none; + = slight; ++ = moderate; +++ = very severe. ASD = atrial septal defect; A-V = atrioventricular; GI = gastrointestinal; LAD = left anterior descending coronary artery; LAFB = left anterior fascicular block; LCA = left main coronary artery; LCx = left circumflex coronary artery; LPFB = left posterior fascicular block; MI = myocardial infarction; N = no or insignificant lesions; Ob = total or near total obstruction; RBBB = right bundle branch block; RCA = right coronary artery; St = 50 percent or greater stenosis.

branch (alternating left anterior and left posterior fascicular block) or evolution toward complete A-V block. Heavy calcifications of the upper part of the interventricular septum and of the left side of the cardiac skeleton were found in three of these four hearts.

Discussion

Few studies have dealt with the pathologic basis of intraventricular conduction disorders. Rossi[7] states in his review that, in the presence of complete left or right bundle branch block, one may anticipate total disruption of the homolateral branch in 67 percent, partial destruction in 20 percent, slight damage in 4 percent and no significant alterations in 9 percent of cases. Bilateral pathologic involvement of the bundle branches may be found in about 50 percent of cases.

We recently studied 10 cases with chronic left anterior fascicular block.[1] In one instance, the anterior fascicle was totally interrupted by a thick fibrous strand while the remainder of the left bundle branch only showed

FIGURE 3. Cases 1 to 9. Schematic sketches of the conduction system in nine hearts with left posterior fascicular block observed during the course of an acute myocardial infarction. **Dotted areas** represent regions with acute lesions; **hatched areas** represent regions with chronic fibrotic lesions. 1 = atrioventricular node; 2 = common His bundle; 3 = right bundle branch; 4 = left bundle branch system.

minor changes. In four cases, severe and scattered alterations were seen to involve the whole left conduction system but the lesions were predominant in the distal portion of the anterior fascicle, which showed subtotal peripheral interruption. In the five remaining hearts, marked disseminated changes were seen at the origin and in the peripheral subdivisions of the left branch. In these cases, the anterior fascicle was neither totally interrupted nor more severely damaged than the rest of the conduction tissue; the centroseptal and posterior fibers were at times at least as severely involved as the anterior fibers.

Incidence of left posterior fascicular block: Few studies dealing with the histopathologic basis of left posterior hemiblock have been published to date, perhaps because of the rarity of this conduction disorder. It seems to be generally agreed that left posterior fascicular block is much rarer and of greater severity than left anterior fascicular block.[2] This observation has been explained by the considerably greater size of the posterior fascicle of the left branch in comparison with its anterior counterpart. Therefore pathologic lesions would theoretically tend to be more extensive to interrupt conduction along the posterior fascicle.

The incidence of left posterior fascicular block is, nevertheless, extremely difficult to assess because the electrocardiographic diagnosis of this condition is so difficult. Rosenbaum et al.[2] stressed from the start that the electrocardiographic signs of left posterior fascicular block are not very specific; for example, they can be encountered in subjects with a slender body build and vertical heart as well as in patients with chronic pulmonary disease. In addition, impairment of conduction along the posterior fibers may manifest itself in some instances by very subtle changes in the surface electrocardiogram.[8] Comparison with previous tracings is often needed to make the diagnosis of left posterior fascicular block because the shift in axis induced by this conduction defect may be trivial in some persons.[9] In the present series, the admission criteria were rather stringent and it is possible that only patients with very severe lesions were selected.

Histopathologic correlates: The few studies of the histopathologic correlates of left posterior fascicular block have indicated the presence of lesions along the posterior fascicle and the mid septal fibers of the left branch.[10–12] Our findings deserve some comments. First, most of our subjects were patients with an acute myocardial infarction. It is well known that, in patients with infarction, a delay of several hours is needed before recognizable histopathologic lesions appear. Myofibrillar degeneration takes 6 hours to develop and coagulation necrosis appears even later.[13] It is therefore not surprising that in two cases in which death took place very soon after the onset of symptoms, no lesions could be found along the posterior fibers. Case 7 is particularly revealing in this respect because left posterior fascicular block appeared in this patient during

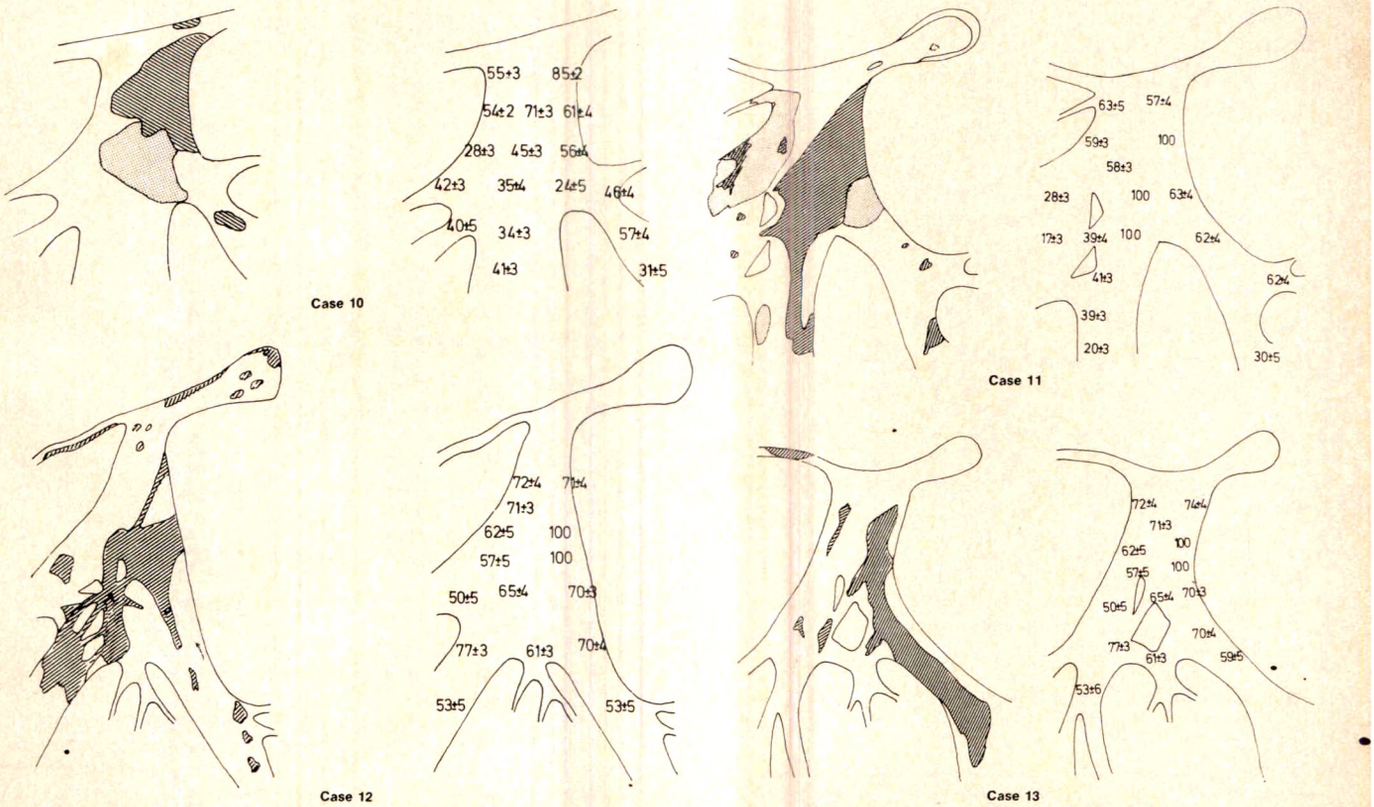

FIGURE 4. Cases 10 to 13. Schematic sketches of the conduction system in four cases with chronic left posterior fascicular block. The value of the relative volumetric density of fibrosis (expressed in percent ±2) is indicated at all levels where it was measured. **Hatched** and **dotted areas** as in Figure 3.

the course of an episode of variant angina leading to ventricular fibrillation. Instances of reversible left posterior fascicular block developing during acute ischemia have previously been described.[14,15]

In our patients with left posterior fascicular block related to myocardial infarction, the coronary arterial lesions were generally very severe in that six had triple vessel disease (of whom three had left main coronary arterial stenosis or obstruction) and two had double vessel disease. Of these nine subjects, at least three had chronic fibrotic alterations of the posterior fibers that in themselves might have accounted for the existence of the left posterior fascicular block. It is likely that the added effect of acute ischemic lesions decreased the number of conducting fibers along the posterior radiation to a critical level that precipitated the functional conduction disorder.

Among the four cases with chronic left posterior fascicular block, three presented very heavy calcifications of the left side of the cardiac skeleton. Lev's disease, which is not frequently found in left anterior fascicular block,[1] was probably the etiologic factor in these three patients. In this small group with chronic left posterior fascicular block, the only patient who had no calcification of the A-V ring and summit of the interventricular septum was found to have diphtheritic myocarditis, a condition known to produce alterations of the conduction tissue.[16,17]

Prognosis: In all cases, whenever the electrocardiograms revealed only isolated left posterior fascicular block, the histopathologic alterations of the specific system, whether acute or chronic, were most severe at the level of the posterior fibers and the posterior aspect of the main left bundle. Compared with the lesions reported in left anterior fascicular block,[1–6] the lesions were less diffuse, more proximal and probably more severe because, in some sites, the relative density of fibrosis reached 100 percent. Some authors[2] have indicated that left posterior fascicular block, especially when associated with right bundle branch block, carries a poorer prognosis in terms of evolution toward complete A-V block. Others[18] have challenged this opinion. If the risk associated with left posterior fascicular block were eventually proved greater, our observations indicate that it is probably not because the underlying lesions are more extensive but because of their more proximal location. Any further extension represents a direct threat to conduction along the main left bundle or even the common His bundle.

Three of our 13 patients had alternating left posterior and left anterior fascicular block. As in the studies of Ohkawa et al.,[19] the three hearts all showed histopathologic changes occurring widely throughout the left-sided conduction system and distributed evenly along the anterior, mid septal and posterior fibers.

Implications: In both acute and chronic situations, left posterior fascicular block is satisfactorily correlated with histopathologic lesions involving the posterior radiation or the posterior part, or both, of the common left bundle. In patients with acute myocardial infarction such block is associated with very severe coronary artery disease, and in our small series, there was a high incidence rate of left main coronary arterial occlusion or stenosis. In patients with chronic disease, it is related to calcifications of the A-V ring and the upper part of interventricular septum. The lesions are less widespread than in left anterior fascicular block but are more severe and more proximal, which may account for their possibly poorer prognosis and easier progression to complete A-V block.

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Incidence, Determinants and Significance of Fixed Retrograde Conduction in the Region of the Atrioventricular Node

Evidence for Retrograde Atrioventricular Nodal Bypass Tracts

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Of 104 consecutive patients studied in our laboratory with His bundle electrograms, atrial and ventricular pacing and the atrial and ventricular extrastimulus techniques, 18 patients in whom the existence and utilization of ventriculoatrial (V-A) bypass tracts were excluded demonstrated evidence for fixed and rapid retrograde conduction in the region of the atrioventricular node (A-V) as suggested by the following: (1) short (36 ± 2 msec [mean ± standard error of mean]) and constant retrograde H_2-A_2 intervals during retrograde refractory period studies; (2) significantly ($P < 0.025$) better V-A than A-V conduction; (3) significantly ($P < 0.025$) shorter retrograde functional refractory period of the V-A conducting system than of the A-V conduction system; and (4) the retrograde effective refractory period of the A-V nodal region was not attainable in any of the 18 patients. Fourteen of the 18 patients (77 percent) had a history of palpitations and 10 (51 percent) had documented paroxysmal supraventricular tachycardia; in 13 (72 percent) single echoes or sustained reentrant supraventricular tachycardia, or both, could be induced during atrial pacing or atrial premature stimulation studies, or both. During tachycardia all these 13 patients had a short (37 ± 2.4 msec) and constant conduction time in the retrograde limb (H-Ae interval) of the reentrant circuit that was identical to the H_2-A_2 interval. In conclusion, fixed and rapid retrograde conduction in the region of the A-V node (1) is seen in approximately 17 percent of patients, (2) is associated with a large incidence of reentrant paroxysmal supraventricular tachycardia, and (3) suggests the presence of A-V nodal bypass tracts (intranodal or extranodal functioning in retrograde manner).

During retrograde studies, some patients demonstrate rapid and fixed retrograde conduction in the region of the atrioventricular (A-V) node whereas the majority demonstrate absence of or slow and variable A-V nodal conduction.[1] The incidence, electrophysiologic determinants and significance of this observation remain unclear. Of 104 consecutive patients studied in our laboratory in whom complete anterograde and retrograde studies were performed, 18 patients demonstrated evidence for fixed and rapid retrograde conduction in the A-V nodal region as suggested by the observation of short and constant retrograde H_2-A_2 intervals during retrograde studies. In this report we discuss the electrophysiologic determinants and the significance of fixed and rapid retrograde conduction in the A-V nodal region in these 18 patients.

Methods

Patients: Electrophysiologic studies were performed with the patients in the postabsorptive nonsedated state after they had received an explanation of the

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nature of the procedure and given signed consent. All cardioactive medications were withheld for at least 4 to 7 days before the study. Of the 18 patients studied, 3 had atherosclerotic heart disease, 3 had hypertension and the remaining 12 had no evident heart disease; their ages ranged from 30 to 79 years. Sixteen of the 18 patients had a normal QRS complex, whereas 1 patient had left bundle branch block and another had right bundle branch block with left axis deviation. The selection of these 18 patients' was based on the finding of fixed and short retrograde H_2-A_2 intervals during retrograde studies at one or more cycle lengths. None of the patients had Wolff-Parkinson-White syndrome, acute myocardial ischemia or infarction or electrolyte or metabolic abnormalities.

In these 18 patients the occurrence of retrograde conduction through the ventricular myocardial-bundle branch-His-atrioventricular nodal axis was confirmed on the basis of the following observations: (1) prolongation of V_2-A_2 or S_2-A_2 intervals during premature ventricular stimulation; (2) the retrograde A_2 deflection never preceded the retrograde H_2 deflection during premature ventricular stimulation but always followed it; and (3) ventricular stimulation during paroxysmal supraventricular tachycardia at a time when the His bundle was refractory did not result in atrial preexcitation.

Electrophysiologic studies: With use of the percutaneous Seldinger technique, quadripolar electrode catheters were positioned under fluoroscopic guidance and electrocardiographic monitoring in the region of the high right atrium, in the right ventricular apex, and in the region of the triscuspid valve for recording His bundle activity[2] in all patients. In seven patients an additional quadripolar catheter was positioned in the region of the coronary sinus. The proximal poles of the atrial and ventricular catheters were utilized for recording and the distal poles for stimulating the respective chambers.

All patients underwent complete anterograde and retrograde studies that included (1) incremental atrial pacing up to the onset of anterograde A-V nodal Wenckebach block or up to heart rates of 200 beats/min; (2) atrial premature stimulation (A_2) studies at one or more cycle lengths (A_1-A_1); (3) coupled atrial premature stimulation during sinus rhythm; (4) incremental ventricular pacing up to rates of 160 to 200 beats/min; and (5) ventricular premature stimulation (V_2 or S_2) studies at one more cycle length (V_1-V_2 or S_1-S_2) identical to the atrial cycle length. Two or more electrocardiographic leads, intracardiac electrograms at filter frequency settings of 40 to 500 hertz and time lines generated at 10, 100 and 1000 msec were displayed simultaneously on a multichannel oscilloscope and recorded on magnetic tape. The records were subsequently replayed on photographic paper at speeds of 150 mm/sec.

Definition of Terms

Anterograde conduction intervals and refractory periods: These were defined as previously described.[3]

Retrograde conduction intervals and refractory periods: *Ventriculoatrial (V-A) conduction time* was measured from the stimulus artifact during ventricular pacing to the onset of the retrograde low septal atrial electrogram in the His bundle tracing.

H_2-A_2 interval was measured from the onset of the His bundle deflection as well as the end of the latter deflection to the onset of retrograde low septal electrogram in the His bundle tracing.

Retrograde functional refractory period of the V-A conduction system, was assessed during (1) incremental ventricular pacing, when it was defined as the shortest ventricular pacing cycle length that resulted in 1:1 V-A atrial conduction, and (2) retrograde refractory period studies, when it was defined as the shortest A_1-A_2 interval in response to any range of V_1-V_2 intervals.

By the latter method it is possible to assess whether the retrograde functional refractory period of the V-A conduction system is determined by the His-Purkinje system (as denoted by S_2-H_2 delays), by the A-V nodal region (as denoted by H_2-A_2 delays) or by both the His-Purkinje and A-V nodal systems (as denoted by both S_2-H_2 and H_2-A_2 delays).

Retrograde effective refractory period of the V-A conduction system was defined as the longest S_1-S_2 (V_1-V_2) interval at which S_2 (V_2) fails to evoke an A_2 response. This variable is determined by the His-Purkinje system when S_2 (V_2) is not followed by an H_2 deflection provided that the latter is identified before block or by the A-V nodal region, in which case the retrograde His bundle deflection (H_2) is not followed by an A_2 deflection.

Retrograde effective refractory period of the A-V nodal region was defined as the longest S_1-H_2 or H_1-H_2 interval at which the H_2 deflection is not followed by an A_2 deflection.

Retrograde functional and effective refractory periods of the His-Purkinje system and the effective refractory period of the ventricular myocardium were defined as previously described.[1,4,5]

Conduction intervals during induced echoes and paroxysmal supraventricular tachycardia: *H-Ae interval* was measured from the onset as well as the end of the His bundle deflection to the onset of the low septal atrial echo in the His bundle tracing.

Ae-H interval was measured from the onset of the low atrial septal echo to the onset of the His bundle deflection during two or more echoes and sustained tachycardia.

H-Ae: Ae-H was expressed as the ratio of these two intervals.[6]

Statistical analysis was performed using Student's *t* test for paired data. All values represent the mean ± standard error of the mean.

Results

Since the selection of these patients was based on the behavior of retrograde conduction in the area of the atrioventricular (A-V) node, retrograde findings are presented first followed by comparative retrograde and anterograde findings.

Retrograde H_2-A_2 intervals: During ventricular premature stimulation studies, the retrograde His bundle deflection (H_1) of of the basic drive beats could not be identified in the majority of patients. However, at closer coupling intervals the retrograde His bundle deflection (H_2) emerged from the V_2 electrogram and was followed by an A_2 deflection (with a low-high sequence that is low septal → coronary sinus → high atrial) in all patients. Thus, the S_2-A_2 (V_2-A_2) intervals could be subdivided into S_2-H_2 and H_2-A_2 intervals, the former representing His-Purkinje conduction and the latter representing conduction in the A-V nodal region. The H_2-A_2 intervals ranged from 25 to 50 msec (mean 36 ± 2 msec) when measured from the onset of the retrograde His bundle deflection to the onset of the earlier retrograde atrial activity, and 10 to 35 msec (mean 22 ± 1.8 msec) (Table I) when measured from the end of the His bundle deflection to the earliest retrograde atrial

activity. For every patient the H_2-A_2 intervals remained remarkably constant for any V_1-V_2 and S_2-H_2 intervals at one or more cycle lengths (Fig. 1).

Comparative retrograde and anterograde conduction patterns (Table I): The shortest V-A interval measured 111 ± 4 msec (range 75 to 135 msec) and the longest V-A interval measured 115 ± 5 msec (range 75 to 160 msec). During incremental ventricular pacing 13 of the 18 patients showed no change in ventricular-atrial intervals up to the maximal paced cycle length (Fig. 2), whereas 3 patients (Cases 12, 13 and 16) demonstrated at 5 msec increase, 2 patients (Cases 9 and 11) a 10 msec increase and 1 patient (Case 7) a 25 msec increase in V-A interval from the longest to the shortest cycle lengths. In the latter patient a retrograde His bundle deflection was discernible during ventricular pacing and the increase in V-A interval was related to the increase in the S-H interval. Fifteen of the 18 patients maintained 1:1 V-A conduction up to maximal paced cycle lengths (average 352 ± 8 msec), and the remaining 3 patients (Cases 6, 10 and 13) demonstrated V-A block at a ventricular pacing cycle length of 375, 400 and 310 msec, respectively.

During sinus rhythm, anterograde A-H intervals ranged from 55 to 110 msec (mean 78 ± 5 msec) and H-V intervals from 35 to 65 msec (average 44 ± 2 msec). In contrast to retrograde conduction all patients demonstrated prolongation of the A-H interval with 1:1 A-V conduction up to atrial pacing cycle lengths of 406 ± 16 msec (range 330 to 600 msec). Anterograde A-V nodal Wenckebach block occurred in all patients at atrial cycle lengths of 300 to 540 msec (average 376 ± 14 msec). Before the occurrence of A-V nodal Wenckebach block the A-H interval demonstrated a 126 ± 21 percent increase over basal A-H intervals. Figure 3 is a representative example demonstrating comparative anterograde and retrograde conduction patterns. At an atrial cycle length of 360 msec A-V nodal Wenckebach occurs whereas 1:1 ventricular atrial conduction is maintained at an identically similar cycle length.

Comparative retrograde and anterograde refractory periods: The retrograde functional refractory period of the ventricular-atrial conducting system as assessed by the ventricular extrastimulus method measured less than 377 ± 7 msec and was determined by the His-Purkinje system in all patients. The functional refractory period of the V-A conducting system as assessed with the ventricular pacing method measured 369 ± 8 msec. The effective refractory period of the V-A conduction system was attained in 12 of the 18 patients and was also determined by the His-Purkinje system (as denoted by V_2-H_2 block). In contrast, the retrograde refractory period of the A-V nodal region was never attained in any of the 18 patients at one or more cycle lengths. Retrograde discontinuous A-V nodal curves were not seen in any patient.

The functional refractory period of the A-V conduction system ranged from 360 to 520 msec (average 406 ± 11 msec in 16 patients), and its exceeded the functional, relative and effective refractory periods of the His-Purkinje system in 16 patients. In the remaining two patients, the functional refractory period of the His-Purkinje system exceeded that of the A-V node. During anterograde studies, discontinuous A-V nodal curves were observed in only 3 patients.

The retrograde functional refractory period of the V-A conducting system as assessed with the extrastimulus method ($P < 0.025$) and as determined with the ventricular pacing method ($P < 0.005$) was significantly shorter than that of the A-V conduction system. In 12 of the 18 patients the functional refractory period of the V-A conduction system was shorter than that of the A-V

TABLE I

Anterograde and Retrograde Conduction Patterns

	Anterograde Conduction (msec)						Retrograde Conduction (msec)					
											H_2-A_2 Intervals	
Case no.	R-R	A-H	H-V	Longest A-H Attained	Shortest ACL for 1:1 A-V	ACL for WB	Shortest V-A Interval	Longest V-A Interval	Shortest VCL for 1:1 V-A	VCL for WB	Onset of H	End of H
1	740	65	35	280	370	360	75	75	330	NA	25	10
2	750	60	35	95	330	300	115	115	360	NA	30	15
3	850	110	40	210	465	430	100	100	375	NA	30	25
4	580	100	50	140	330	300	110	110	300	NA	30	15
5	710	75	40	180	430	400	110	110	350	NA	35	25
6	650	75	35	120	400	375	100	100	400	375	50	35
7	900	105	60	130	400	350	135	160	370	NA	50	35
8	670	75	40	135	370	340	130	130	370	NA	50	30
9	970	75	40	190	350	320	95	105	370	NA	25	15
10	960	100	40	350	480	440	130	130	440	400	50	35
11	960	60	50	115	460	430	130	140	380	NA	30	20
12	820	80	50	185	430	400	90	95	380	NA	35	20
13	740	55	40	110	330	310	120	125	330	310	30	15
14	610	55	40	200	400	375	120	120	300	NA	30	15
15	720	60	40	120	400	410	110	110	300	NA	40	20
16	640	90	45	185	400	380	110	115	350	NA	35	20
17	760	110	65	120	600	540	125	125	380	NA	40	25
18	640	60	45	190	335	320	90	90	370	NA	30	15

ACL = atrial cycle length; A-V = atrioventricular; H = His bundle deflection; NA = not available; VA = ventriculoatrial conduction; VCL = ventricular cycle length; WB = Wenckebach block.

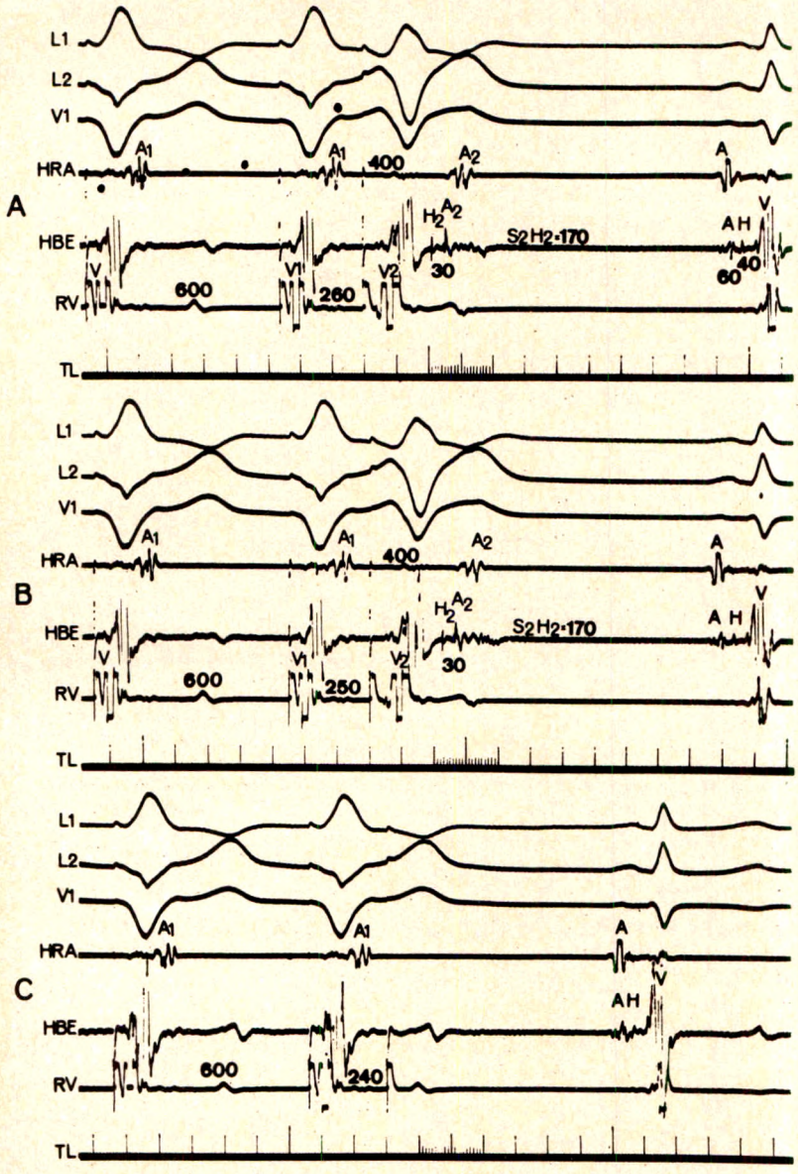

FIGURE 1. Retrograde conduction in the region of the atrioventricular (A-V) node (H_2–A_2 intervals) during premature ventricular stimulation. **From top to bottom in each panel,** L_1, L_2, V_1 = surface electrocardiographic leads I, II and V; HRA = high right atrial electrogram; HBE = His bundle electrogram; RV = right ventricular electrogram; TL = time lines at 10, 100 and 1,000 msec. In all panels the right ventricle is stimulated at a basic cycle length of 600 msec. **A,** a premature stimulus introduced at an S_1-S_2 interval of 260 msec results in retrograde conduction through the His-Purkinje (S_2-H_2 = 170 msec) and A-V nodal axis. The retrograde A_2 has a low-high sequence and follows the retrograde H_2 deflection with a short H_2-A_2 interval of 30 msec. **B,** as the S_1-S_2 interval is decreased to 250 msec the H_2-A_2 interval stays constant at 30 msec. **C,** at an S_1-S_2 interval of 240 msec the ventricular myocardium is refractory.

conduction system (Fig. 4); in 3 patients it was equal to that of the A-V conduction system and in the remaining 3 patients it was longer than that of the A-V conduction system. In three of the six patients whose functional refractory period of the V-A conduction system was equal to or shorter than that of the A-V conduction system the full range of retrograde A_1-A_2 intervals could not be assessed by the ventricular extrastimulus technique because of attainment of the retrograde effective refractory period of the His-Purkinje system.

Incidence of palpitations and the laboratory induction of tachyarrhythmias (Table II): Fourteen of the 18 patients (78 percent) gave a history of palpitations with electrocardiographic documentation of paroxysmal supraventricular tachycardia in 10 (51 percent). In four patients (22 percent) atrial echoes and in nine patients (50 percent) sustained paroxysmal supraventricular tachycardia of the reentrant type could be induced during electrophysiologic studies. In addition, in one patient short unsustained paroxysms of atrial fibrillation were induced during atrial premature stimulation studies. Thus, in 72 percent of these patients atrial echoes or paroxysmal supraventricular tachycardia, or both, was inducible.

The mode of induction of atrial echoes or tachycardia or both, included one or more of the following: (1) atrial pacing-induced A-V nodal Wenckebach periods, (2) premature atrial stimulation at a fixed basic cycle length, and (3) coupled atrial stimulation. In contrast, atrial echoes or paroxysmal supraventricular tachycardia, or both, could not be induced in any of these patients during (1) incremental ventricular pacing, (2) interruption of ventricular pacing, or (3) ventricular extrastimulation.

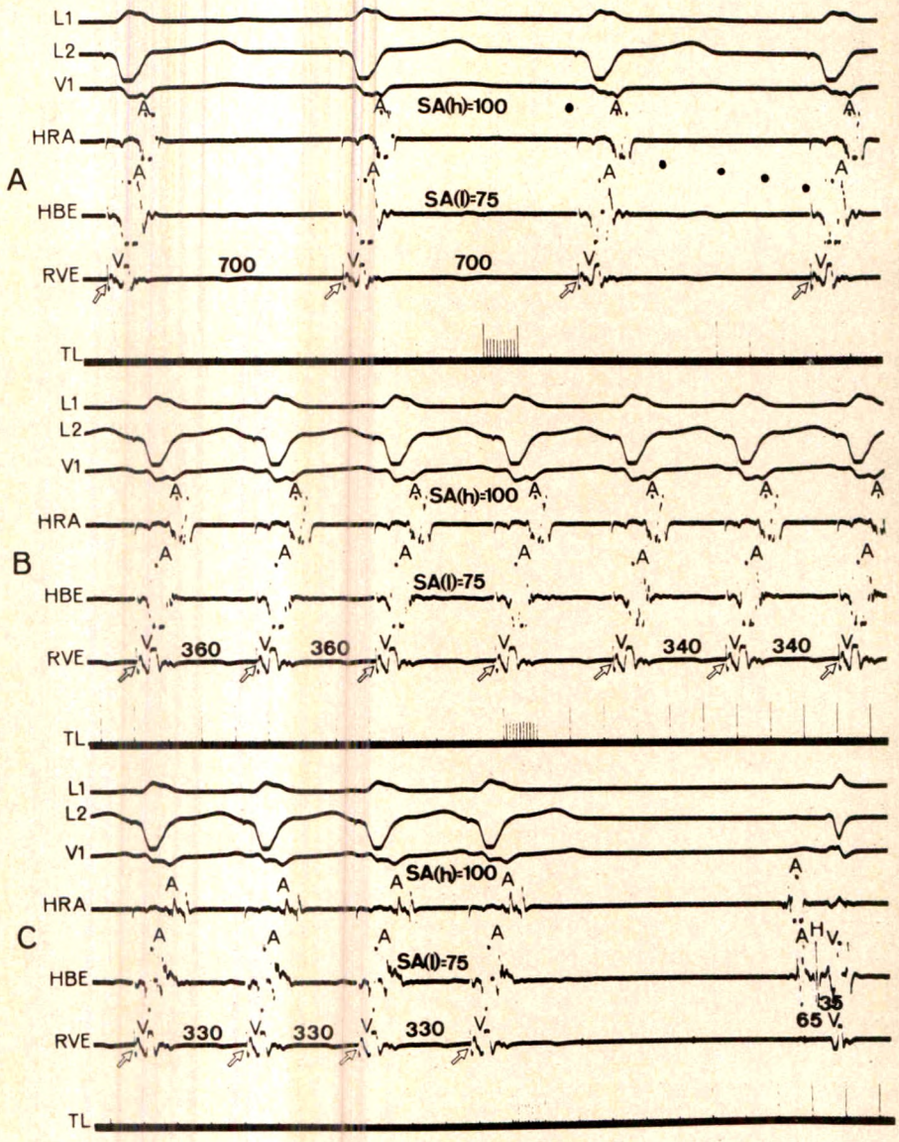

FIGURE 2. Effect of incremental ventricular pacing on the ventriculo atrial (V-A or S-A) intervals. RVE = right ventricular electrogram. Other abbreviations as in Figure 1. **A**, the right ventricle is paced at a basic cycle length of 700 msec, which results in 1:1 retrograde conduction to the atria with an S-A interval of 100 msec and 75 msec measured to the onset of the high and low atrial electrogram, respectively. **B**, ventricular pacing at cycle lengths of 360 to 340 msec does not alter the V-A or S-A intervals with maintenance of 1:1 V-A conduction. **C**, ventricular pacing at the shortest cycle length of 330 msec results in similar S-A intervals with 1:1 V-A conduction as seen in panels **A** and **B** without the occurrence of V-A block.

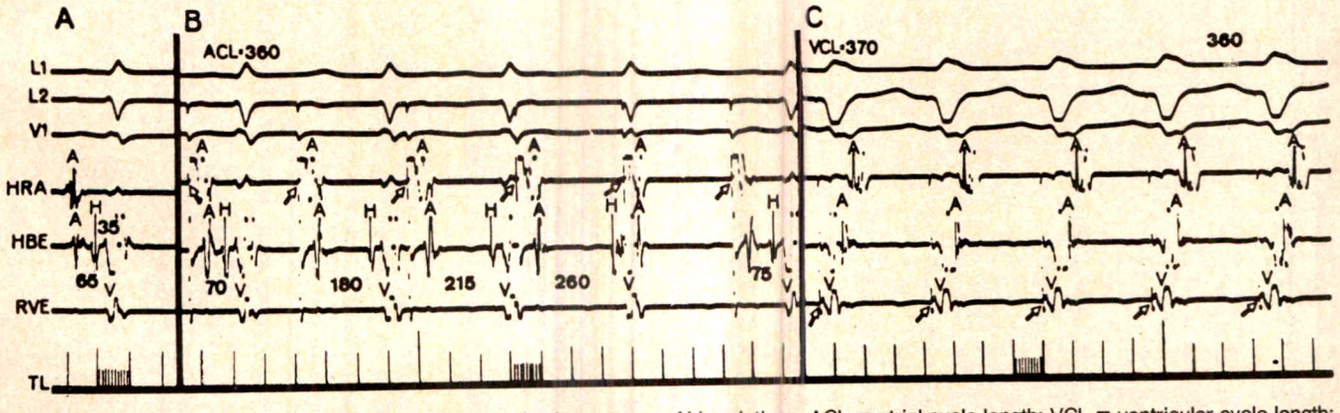

FIGURE 3. Comparative anterograde and retrograde conduction patterns. Abbreviations: ACL = atrial cycle length; VCL = ventricular cycle length; other abbreviations as in Figures 1 and 2. **A**, a sinus beat. The A-H interval is 65 msec and the H-V interval is 35 msec. **B**, at an atrial cycle length of 360 msec, A-V nodal Wenckebach block results with a 5:4 conduction ratio. **C**, 1:1 V-A or S-A conduction is maintained during ventricular pacing at ventricular cycle lengths of 370 and 360 msec.

Characteristics of atrial echoes and paroxysmal supraventricular tachycardia (Table II): The A-H intervals at which atrial echoes or paroxysmal supraventricular tachycardia, or both, was induced ranged from 175 to 445 msec. The most striking feature of the atrial echoes and tachycardia were the intervals from the His bundle deflection to the earliest point of retrograde atrial activation, that is, the H-Ae intervals.

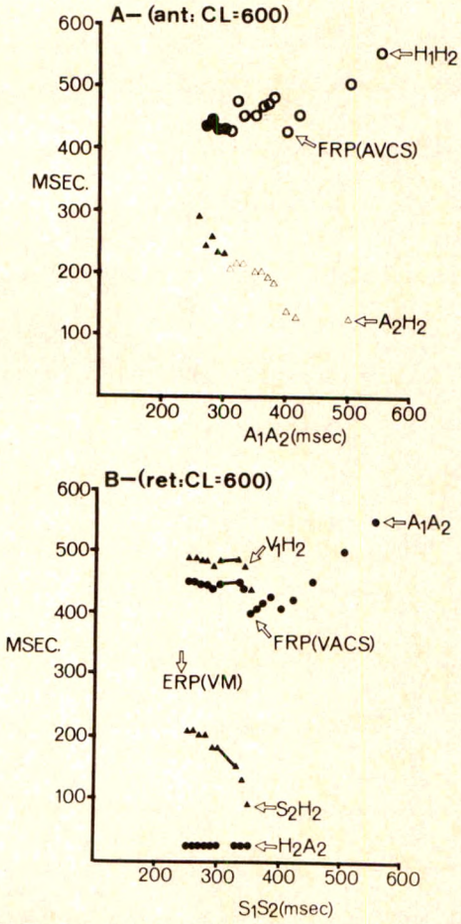

FIGURE 4. Comparative anterograde (ant.) atrioventricular conduction system (AVCS) and retrograde (ret) ventriculoatrial conduction system refractory period patterns in the same patient at a cycle length (CL) of 600 msec. **A**, anterograde H_1-H_2 and A_2-H_2 curves in response to decreasing A_1-A_2 intervals. **Abscissa** = A_1-A_2 intervals; **ordinate** = H_1-H_2 and A_2-H_2 intervals. The **open circles** represent H_1-H_2 intervals without atrial echoes and the **closed circles** H_1-H_2 intervals with atrial echoes. The **open triangles** represent A_2-H_2 intervals without atrial echoes and the **closed triangles** critical A_2-H_2 intervals for atrial echoes. The functional refractory period (FRP) of the atrioventricular system is 440 msec. **B**, A_1-A_2, V_1-H_2, S_2-H_2 and H_2-A_2 curves at decreasing S_1-S_2 intervals. **Abscissa** = S_1-S_2 intervals; ordinate = A_2-A_2, V_1-H_2, S_2-H_2 and H_2-A_2 intervals. As the S_1-S_2 intervals are decreased, there is a decrease in A_1-A_2 intervals until the retrograde (ret.) His bundle deflection (H_2) emerges from the ventricular electrogram. The A_1-A_2 curve then stays level and is parallel to the V_1-H_2 curve (retrograde His-Purkinje). The plateau of the A_1-A_2 curve is related to prolongation of S_2-H_2 intervals (bundle branch–His-Purkinje delay) whereas the retrograde H_2-A_2 intervals stay fixed at all S_1-S_2 and V_1-H_2 intervals. Also note that the retrograde functional refractory period of the ventriculoatrial conduction system (VACS) is shorter (380 msec) than that of the atrioventricular conduction system. ERP (VM) = effective refractory period.

These features included: (1) The H-Ae intervals measured 37 ± 2.4 msec (range 25 to 50 msec) from the onset and 21 + 2.1 msec (range 10 to 35 msec) from the end of the His bundle deflection. The low septal atrial electrogram of the echo beat preceded the coronary sinus electrogram in all patients and the V deflection both on the His bundle tracing as well as on the right ventricular tracing in the majority of patients (Fig. 5); (2) the H-Ae intervals were always significantly shorter than the corresponding Ae-H intervals such that the H-Ae: Ae-H ratios were > 1:4.77 (range 1:4.77 to 1:11.1) and the reverse never occurred: (3) in individual patients the H-Ae intervals remained unchanged during repeated inductions of atrial echoes or tachycardia and were independent of the variations of both Ae-H intervals and the rates of tachycardia; and (4) the H-Ae intervals were significantly shorter than the A-H interval ($P < 0.001$) measured during sinus rhythm.

In the four patients in whom paroxysmal supraventricular tachycardia was not sustained the retrograde echo always blocked in the anterograde limb that is, the retrograde echo was not conducted to the His bundle (Ae-H block).

H-Ae and H_2-A_2 correlations: In all patients in whom atrial echoes or paroxysmal supraventricular tachycardia, or both, were induced, there was a remarkable and striking relation between the H-Ae and retrograde H_2-A_2 intervals measured during premature ventricular stimulation in the following manner: (1) The H-Ae and H_2-A_2 intervals were identical in all patients (Fig. 6 and 7, Table II), and (2) the retrograde low septal atrial echo was identical in its initial deflection, and total configuration to the retrograde low septal A_2 deflection in all patients in whom an atrial echo was clearly discernible in the His bundle tracing.

Discussion

Our findings indicate that the incidence rate of short and fixed retrograde conduction in the region of the A-V node (that is, short and fixed H_2-A_2 intervals) is approximately 17 percent. Of additional interest was the observation of a large incidence of palpitations and the ability to induce either atrial echoes or paroxysmal supraventricular tachycardia during intracardiac stimulation studies.

Electrophysiologic evidence for selective utilization of a fast pathway for retrograde propagation: The electrophysiologic findings in these patients indicate that the A-V node was utilized for anterograde conduction as suggested by the well known relation between decreases in cycle length and increase in conduction time within the A-V node. Selective utilization of a "fast" pathway for retrograde propagation is suggested by the following: (1) no appreciable change in V-A intervals with maintenance of 1:1 V-A conduction up to maximally paced ventricular rates (170 to 200 beats/min) in the majority of patients. Previous studies on the patterns of anterograde and retrograde conduction in man have also led to similar observations. Narula[7] reported 1:1 ventricular-atrial conduction with unchanging V-A intervals in 19 of 124 patients (15

TABLE II

Characteristics of Paroxysmal Supraventricular Tachycardia

Case no.	Induction of Atrial Echo(+) or PVST(++)	A-H interval for Atrial Echoes and/or PSVT	Average Rate of PSVT	Average Ae-H Interval	H-Ae interval		H-Ae/Ae-H Ratio	H_2-A_2 interval	
					Onset of H	End of H		Onset of H	End of H
1	+	230–290	. . .	. . .	25	10	. . .	25	10
2	++	175–180	295	265	30	10	1:8.83	30	15
3	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
4	++	180	314	284	30	15	1:9.46	30	15
5	++	290–310	380	350	35	25	1:10	35	25
6	++	260–375	288	238	50	35	1:4.76	50	35
7	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
8	++	280–300	354	308	50	30	1:6.16	50	30
9	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
10	++	330–445	440	395	50	30	1:7.9	50	35
11	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
12	+	205–210	. . .	270	35	20	1:7.71	35	20
13	+	230–255	. . .	. . .	30	15	. . .	30	15
14	++	220–295	363	333	30	20	1:11.1	30	15
15	++	315	335	310	40	20	1:7.75	40	20
16	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
17	++	310–400	410	370	40	25	1:9.25	40	25
18	+	220	. . .	. . .	30	15	. . .	30	15

H = His bundle deflection; PSVT = paroxysmal supraventricular tachycardia.

percent) although the maximal pacing rates were generally lower than those utilized in our study. The V-A intervals in Narula's study (176 ± 27 msec) are not directly comparable with those measured in our study (111 ± 4 msec) because in his study these intervals were measured from a point in the right ventricular apex to one in the high right atrium, a measurement that included intraatrial conduction time. Narula postulated the utilization of A-V nodal bypass tracts for retrograde propagation, although the presence of a functional V-A bypass tract (Kent bundle) was not excluded. Schuilenberg[8] observed that 11 percent of patients with intact V-A conduction had no change in ventricular interval whereas 88 percent of patients demonstrated a progressive increase in this interval during incremental ventricular pacing. However, he did not report the actual values for the V-A interval.

The other findings suggesting a "fast" pathway for retrograde conduction are: (2) constant and fixed retrograde H_2-A_2 interval over a wide range of V_1-V_2 (S_1-S_2) and V_1-H_2 intervals; (3) the functional refractory period of the fast retrograde pathway as determined with the ventricular extrastimulus method and with the ventricular pacing method was significantly shorter than that of the anterograde pathway (that is, the A-V node); and (4) the retrograde effective refractory period of the retrograde fast pathway was not attained in any patient whereas that of the anterograde pathway (that is, the A-V node) was attained in the majority in the anterograde direction. This observation could be related to the fact that during retrograde refractory period studies conduction delay occurred solely within the His-Purkinje segment (S_2-H_2 delays) of the V-A conduction system so that the S_1-H_2 or H_1-H_2 intervals were longer than the anterograde A_1-A_2 intervals. However, because in the majority of patients 1:1 V-A conduction was maintained without the occurrence of V-A block at even shorter pacing cycle lengths when similar or longer atrial cycle lengths produced A-V nodal Wenckebach block, the effective refractory period of the

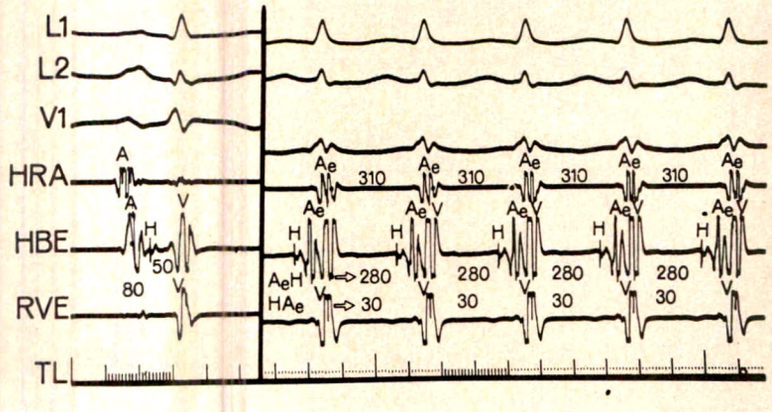

FIGURE 5. Characteristics of paroxysmal supraventricular tachycardia. **Left panel,** a sinus beat. The A-H interval is 80 msec and the H-V interval is 50 msec. **Right panel,** paroxysmal supraventricular tachycardia with a cycle length of 310 msec. The retrograde low septal echo precedes the V deflection in the His-bundle and right ventricular electrograms. The H-Ae interval is 30 msec and the Ae-H interval is 280 msec. Abbreviations as in Figures 1 and 2.

retrograde fast pathway in all likelihood is shorter than that of the anterograde slow pathway.

It may be argued that both the slow and fast pathways are utilized intermittently for both anterograde and retrograde conduction as proposed by the theory of dual A-V nodal pathways (functional A-V nodal dissociation).[9–13] In contrast to the theory of dual A-V nodal pathways, we found that (1) the retrograde fast pathway was never utilized for anterograde conduction, (2) the slow pathway was never utilized for retrograde conduction, (3) the functional refractory period of the slow pathway was longer than that of the retrograde fast pathway, (4) the effective refractory period of the retrograde fast pathway was never attained, and (5) during induced atrial echoes and tachycardia the fast retrograde pathway was always utilized selectively for retrograde conduction and the reverse was never observed.

Characteristics of atrial echoes and paroxysmal supraventricular tachycardia: Atrial echoes and paroxysmal supraventricular tachycardia could be induced in 22 and 50 percent of our patients, respectively. Although no systematic study has assessed the laboratory induction of atrial echoes and paroxysmal supraventricular tachycardia in patients with short and fixed retrograde H_2-A_2 intervals, Narula[7] observed that 47 percent of patients with intact V-A conduction and unchanging V-A intervals had paroxysmal supraventricular tachycardia. The characteristics of tachycardia and the correlations between retrograde H_2-A_2 values and H-Ae intervals were not available in Narula's study. In contrast, Schuilenberg[8] found no evidence of palpitations or supraventricular tachycardia in any of his patients with intact V-A conduction and unchanging ventricular atrial intervals. However, Schuilenberg did not indicate his patients had, in fact, remarkably short V-A intervals and short constant H_2-A_2 intervals.

The observation that the H-Ae intervals were identical to the retrograde H_2-A_2 interval is of additional interest, and it strongly suggests that the pathway utilized for retrograde conduction during ventricular stimulation studies is identical to the fast pathway utilized during tachycardia. Furthermore, the observation that the retrograde fast pathway during induced echoes and tachycardia was independent of the mode of induction, the A-H intervals required for induction, the corresponding Ae-H intervals and the rate of tachycardia is akin to the electrophysiologic characteristics of the retrograde pathway as determined during retrograde studies. These findings suggest that the fast pathway during tachycardia is solely and selectively utilized for retrograde propagation and that the distal limb of this pathway connects to the bundle of His.

The findings that neither tachycardia nor ventricular echoes could be induced in any of our patients during retrograde studies is of additional interest. One or both of the following possibilities could be provided for the latter observation: (1) It is possible that during retrograde conduction there is concealment within the slow pathway (A-V node), making it refractory for anterograde conduction, and (2) rapid and fixed conduction through the fast pathway (that is, unchanging V-A conduction and H_2-A_2 interval) does not provide sufficient retrograde delay for anterograde turnaround of the impulse that encounters the refractory A-V node. It should be pointed out that in the four patients in

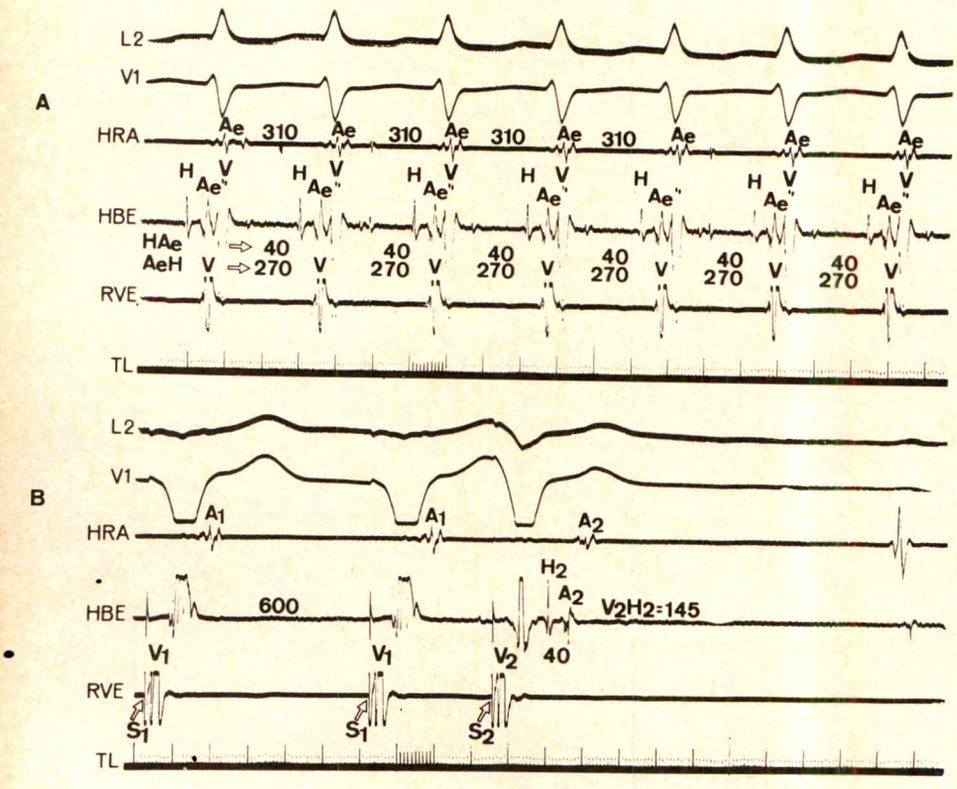

FIGURE 6. Relation between the H-Ae interval during tachycardia and the H_2-A_2 interval during retrograde studies. **A**, paroxysmal supraventricular tachycardia with a cycle length of 310 msec. The Ae-H interval is 270 msec and the H-Ae interval is 40 msec. The retrograde low septal atrial echo clearly precedes the V deflection in the His bundle and right ventricular electrograms. **B**, same patient. Retrograde studies at a basic cycle length of 600 msec. There is a retrograde atrial activation sequence during the basic drive. At an S_1-S_2 interval of 330 msec there is retrograde conduction through the bundle branch–His-atrioventricular nodal axis with a V_2-H_2 interval of 145 msec and an H_2-A_2 interval of 40 msec. The H_2-A_2 interval is identical in duration to the H-Ae interval and the retrograde A_2 deflection is identical in its initial deflection and total configuration to the low septal Ae deflection. Abbreviations as in Figures 1 and 2.

whom atrial echoes could be initiated during anterograde studies and tachycardia could not be sustained, the retrograde echo always blocked in the slow pathway (Ae-H block). Also, these patients had remarkably short H-Ae and H_2-A_2 intervals (onset of H = 25 to 30 msec, end of H = 10 to 15 msec). Akhtar et al.[14] demonstrated that ventricular echoes due to A-V nodal reentry occurred in patients with V_2-A_2 delays in whom the delay occurred in the H_2-A_2 segment. The absence of delay in the fast pathway in our patients during retrograde studies provided the basis for the inability to initiate tachycardia or ventricular echoes of the A-V nodal type during retrograde studies. This observation of itself provides further evidence that conduction in the retrograde fast pathway was fixed.

The inability to induce echoes and supraventricular tachycardia in 28 percent of these patients is most likely related to the fact that a critical balance between conduction and refractoriness must exist within both the anterograde and retrograde limbs of a reentrant circuit for reentry to occur. It is likely that a critical degree of A-H delay required for induction of echoes and/or tachycardia was not attained in these patients. In three of these four patients the effective refractory period of the A-V node was 360, 380 and 290 msec, respectively. It is possible that atropine may have altered conduction and refractoriness of the anterograde pathway such that tachycardia may have been inducible.[15] However, this possibility was not tested in this study.

The anatomic substrate of the retrograde limb: Our findings suggest that the retrograde pathway in the region of the A-V node is (1) an extranodal tract functional only in the retrograde direction, or (2) an intranodal tract that is insulated from the rest of the A-V nodal mass and selectively conducts in retrograde fashion. However, the observation that the retrograde H_2-A_2 intervals were identical in duration and electrophysiologic behavior to the H-Ae intervals and that the configuration of the retrograde A_2 deflection was the same as that of the retrograde low septal echo supports the former (1) rather than the latter (2) possibility. If the reentrant circuit was intranodal, then the H-Ae interval would have been shorter than the retrograde H_2-A_2 intervals. However, if the intranodal pathway was connected to the His bundle with the turnaround of the impulse occurring at the level of the His bundle, then

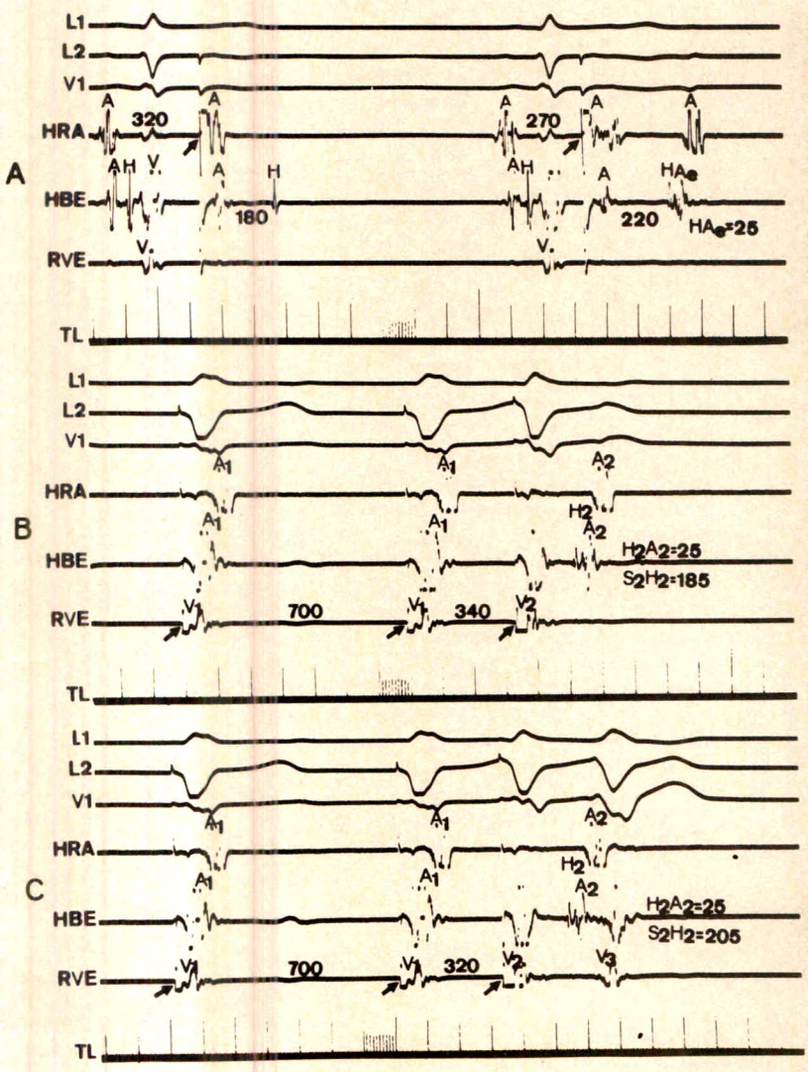

FIGURE 7. Relation between the H-Ae interval during single induced echoes and the H_2-A_2 interval during retrograde studies. **A**, coupled atrial stimulation during sinus rhythm. At a coupling interval of 320 msec the A-H interval is 180 msec with block below the His bundle. The coupling interval of 270 msec results in an A-H interval of 220 msec and an atrial echo response is seen with an H-Ae interval of 25 msec. Block below the His bundle persists. **B**, same patient. The right ventricle is stimulated at a basic cycle length of 700 msec with retrograde atrial capture. A premature stimulus introduced at a coupling interval of 340 msec results in retrograde conduction to the atrium with a S_2-H_2 interval of 185 msec and an H_2-A_2 interval of 25 msec identical to the H-Ae interval in **A**. **C**, at a coupling interval of 320 msec the S_2-H_2 interval is 205 msec whereas the H_2-A_2 interval of 25 msec is identical to the H-Ae interval. A third beat (V_3) follows, which is due to reentry within the bundle branch–His-Purkinje system. The retrograde A_2 deflection in **B** and **C** is identical in its initial deflection and total configuration to the low septal atrial echo (Ae). Abbreviations as in Figures 1 and 2.

the H-Ae interval would have been identical to the retrograde H_2-A_2 interval. The exact incidence of the presence of an A-V nodal bypass tract (extranodal or intranodal) as a substrate for the initiation of reentrant tachycardias in and around the A-V junction is not known. However, previous studies on the effects of digitalis[16] and verapamil[17] on the properties of the limbs of the anterograde and retrograde tachycardia have implicated an A-V nodal bypass tract as the retrograde limb of the tachycardia.

Although it is difficult to draw strong anatomic correlations from electrophysiologic findings in the absence of anatomic studies in these patients, current information suggests that the location of these tracts may be one of the following: (1) an intranodal tract that connects to the His bundle and is insulated from the rest of the A-V nodal mass; (2) His-atrial,[18,19] (3) atrio-nodal tracts bypassing the A-V node,[20] or (4) atrial fibers entering the lower endocardial surface of the A-V node in close proximity to the His bundle.[21] The presence of A-V nodal bypass tracts (intranodal or extranodal) functioning in retrograde manner could provide the substrate for the initiation and sustenance of reentrant supraventricular tachycardia as seen in patients with the Wolff-Parkinson-White syndrome and in those with concealed V-A bypass tracts.

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Reciprocal Tachycardias Using Accessory Pathways With Long Conduction Times

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Three patients with reentrant tachycardia are described who had an accessory pathway with a very long conduction time that was incorporated in the tachycardia circuit. The accessory pathway was able to conduct in one direction only, in retrograde manner in two patients and in anterograde manner in the remaining patient. Evidence is presented that reveals that in the first two patients the accessory pathway was septally located, had completely bypassed the normal atrioventricular (A-V) conduction system, had properties of decremental conduction, and had an atrial exit close to the coronary sinus and a ventricular exit relatively far from the atrioventricular A-V ring. In the third patient, who manifested wide QRS complex during tachycardia, the ventricular end of the accessory pathway seemed to be located close to the right ventricular apex. The atrial end of the pathway could not be localized exactly.

The existence of accessory atrioventricular (A-V) connections has been well documented during the past decade.[1–4] These accessory pathways are responsible for the electrocardiographic features in patients with the Wolff-Parkinson-White (WPW) syndrome and are utilized in the most frequent form of tachycardia observed in these patients, the so-called circus movement tachycardia.[2,5–7] Accessory A-V pathways capable only of retrograde (ventriculoatrial) conduction have been shown to participate in the mechanism of circus movement tachycardias in patients without electrocardiographic manifestations of Wolff-Parkinson-White conductions.[6,8–12] These accessory pathways (overt and concealed) characteristically have conduction times that are shorter than those over the normal A-V nodal–His-Purkinje pathway.

In this article we describe a different type of accessory pathway with very long conduction times, longer than those over the A-V nodal–His-Purkinje pathway. These accessory pathways were found to be part of a reentrant circuit in three patients with A-V junctional circus movement tachycardia. In two of these patients the accessory pathway with a long conduction time was used in the retrograde manner, the tachycardia being of the type previously described by Coumel et al.[13] as the "permanent" or "incessant" form of A-V junctional reciprocating tachycardia. In the third patient this slowly conducting accessory pathway was used in the anterograde manner resulting in a junctional circus movement tachycardia with wide QRS complexes.

Methods

Clinical characteristics of the three patients are given in Table I. After giving informed consent all patients underwent an electrophysiologic study in the postabsortive state. No patient was receiving medication at the time of the investigation. Electrophysiologic studies were performed according to techniques previously described.[14] Leads I, II, III, V_1 and V_6 were simultaneously recorded with bipolar electrograms from the high right atrium, coronary sinus and His bundle region, except in Patient 3, in whom the only available intracavitary leads

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TABLE I

Clinical and Electrocardiographic Characteristics of the Three Patients Studied

	Patient 1	Patient 2	Patient 3
Sex	M	F	F
Age (yr)	9	26	30
Heart rate/min during tachycardia	125–180	125–170	145–155
QRS width (msec) during tachycardia	80	100	130
Frontal QRS axis during tachycardia	+45°	+30°	−60°
P-R/R-P ratio during tachycardia	0.31	0.48	?

P-R/R-P = ratio between P-R and R-P interval during tachycardia.

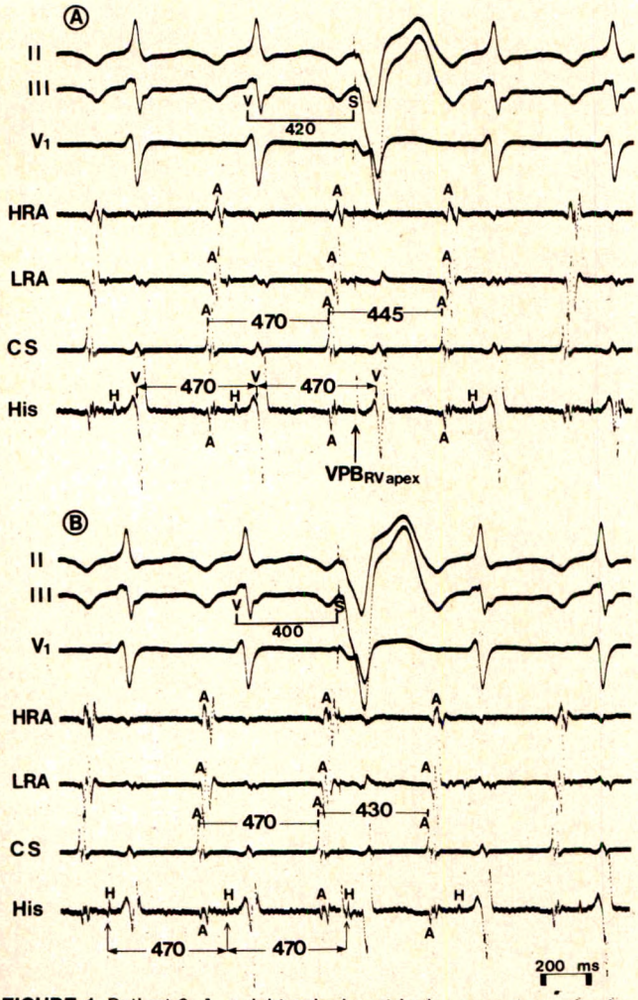

FIGURE 1. Patient 2. **A,** a right apical ventricular premature stimulus (VPB_{RVapex}) given during tachycardia 420 msec after the QRS complex advances subsequent atrial activity by 25 msec, without advancing the ventricular electrogram in the His bundle electrogram. **B,** a right apical ventricular premature stimulus (S) given during tachycardia 400 msec after the QRS complex advances atrial activity by 40 msec, without disturbing anterograde His bundle activation. Leads II, III, V_1, high right atrium (HRA), low right atrium (LRA), coronary sinus (CS) and bundle of His (His) electrograms were simultaneously recorded. A = atrium; H = bundle of His; V = ventricle; ms = milliseconds.

were recorded in the high right atrium and His bundle. In Patient 2 recordings from the low lateral atrium were also obtained.

A programmable electrical stimulator (Janssen Pharmaceutica, Belgium) was used that delivered impulses with a duration of 2 msec at twice diastolic threshold. All data were directly recorded on a multichannel ink-jet recorder (Mingograf, Siemens-Elema, Sweden), and in Patients 1 and 2 this information was also stored on magnetic tape (Ampex PR-2200).

Results

Patients 1 and 2

Spontaneously recurring A-V junctional circus movement tachycardia: Patients 1 and 2 had a chronic, almost continuous, supraventricular tachycardia. Spontaneous variations in the cycle length of the tachycardia were observed in both patients. These changes were mainly the result of variations in ventriculoatrial (V-A) time, although slight changes (± 10 msec) in the A-H time were observed as well. In both patients the earliest atrial activity during tachycardia was recorded in the proximal coronary sinus (Fig. 1). This atrial electrogram was closely followed (5 to 10 msec later) by the low right septal atrial activity as recorded in the His bundle electrogram. During tachycardia P waves were negative in leads II, III and V_2 to V_6 in both patients. Characteristically the P-R interval was shorter than the R-P time. Some spontaneous terminations of the arrhythmias were observed, particularly in Patient 1. During sinus rhythm the P-A time was 30 msec in both patients; the A-H interval measured 70 msec in Patient 1 and 80 msec in Patient 2. The H-V times were, respectively, 40 and 50 msec.

Observations during spontaneous initiation of the tachycardia: Several episodes of spontaneous initiation of tachycardia were observed in both patients during the electrophysiologic study, and most frequently in Patient 1. Although a tendency for shortening of the sinus cycle length was observed before spontaneous initiation of tachycardia, neither a critical number of sinus beats nor a critical shortening of the sinus cycle length preceded the spontaneous initiation of the arrhythmia.

The initial V-A time at spontaneous initiation of tachycardia was occasionally shorter than that measured with subsequent tachycardia beats but generally no change in V-A time or only a 10 msec difference was observed particularly in Patient 1. The A-H interval of the first tachycardia beat was almost identical (±10 msec) to the A-H interval of the preceding sinus cycle and tended to remain constant when spontaneous changes in the tachycardia cycle length were absent.

Effects of ventricular premature stimuli during tachycardia: *On giving a single right apical ventricular premature impulse during tachycardia we observed the following:*

1. In Patient 2 a single right apical ventricular premature beat delivered late in the tachycardia cycle was able to advance subsequent atrial activity by 25 msec without advancing the local ventricular electrogram in the His bundle lead (Fig. 1, panel A). This advanced atrial activity had an identical sequence of atrial activation to that observed during tachycardia.

2. In both patients, adequately timed single ventricular premature stimuli advanced atrial activity (with the same sequence as that during tachycardia) at a time when the His bundle was refractory (Fig. 1, panel B).

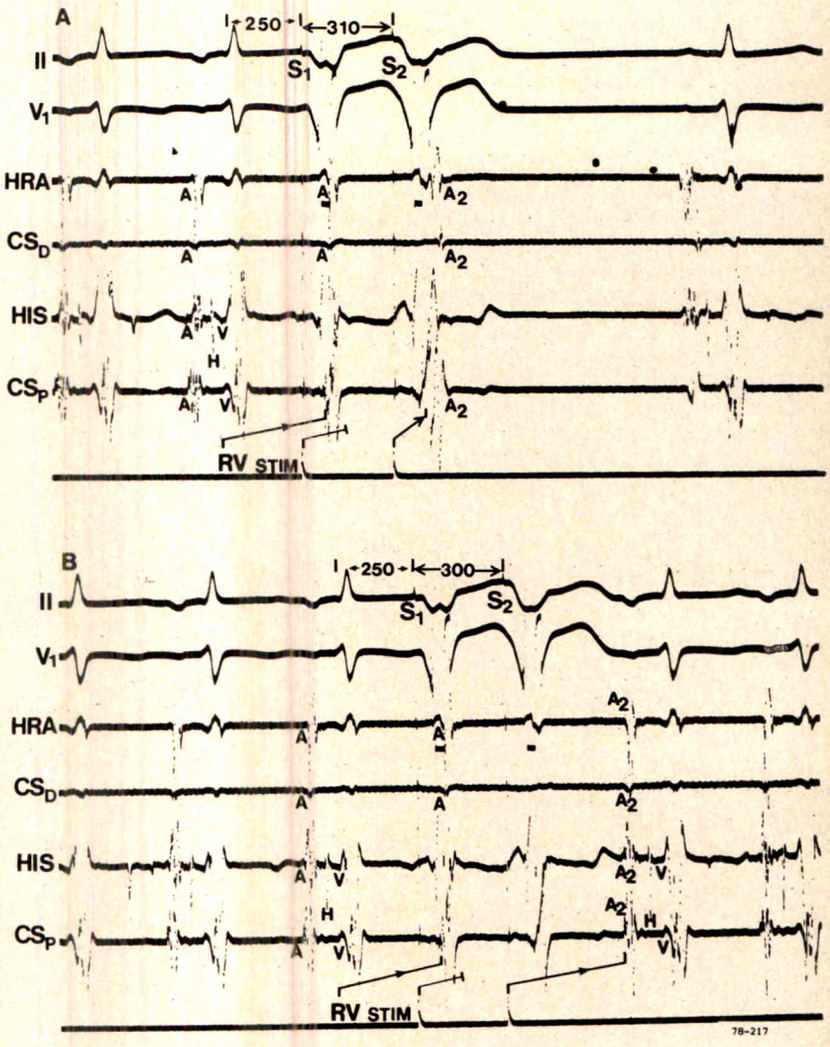

FIGURE 2. Patient 1. **A,** of two right ventricular premature stimuli (RVSTIM) (S_1, S_2) given after 250 msec and 310 msec, respectively, the first shows block in ventriculoatrial conduction, the second is conducted in retrograde manner over the atrioventricular node (A_2). **B,** advancing the second ventricular premature stimulus (S_2) by 10 msec results in retrograde block in the atrioventricular node, exclusive prolonged ventriculoatrial conduction over the accessory pathway (A_2) and reinitiation of tachycardia. CS_D and CS_p = distal and proximal coronary sinus, respectively; other abbreviations as in Figure 1.

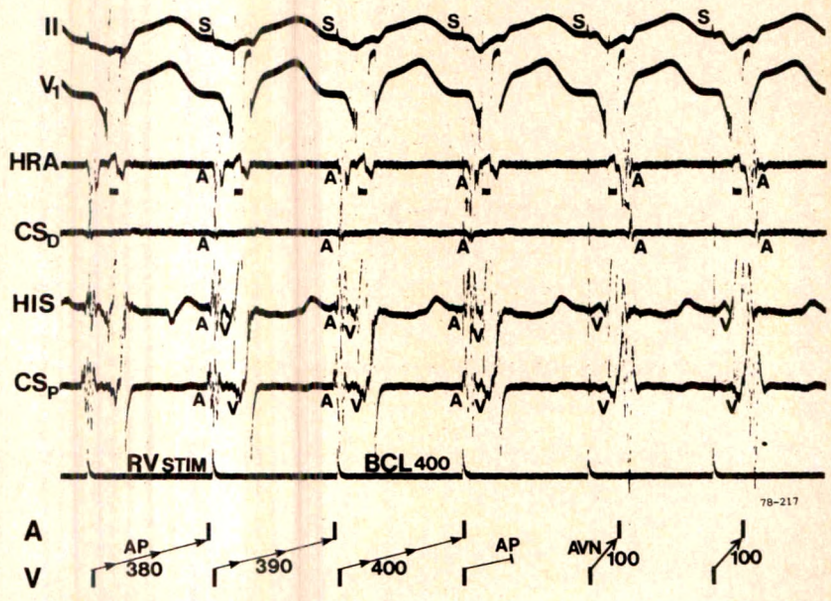

FIGURE 3. Patient 1. Effect of regular ventricular pacing at a rate of 150/min. Note that ventriculoatrial conduction over the accessory pathway (AP) shows progressive prolongation and is followed by block in the accessory pathway. The next two ventricular complexes are conducted to the atrium over the atrioventricular node (AVN). BCL = basic cycle length; other abbreviations as in Figures 1 and 2.

3. In both patients, an appropriately timed ventricular premature beat could reproducibly terminate the tachycardia whenever this ventricular paced impulse was not followed by atrial activity.

4. V-A time after single ventricular premature stimuli delivered during tachycardia showed slight progressive prolongation on increasing the prematurity of the ventricular test impulse. This finding was more evident in Patient 2 because the retrograde effective refractory period of the accessory pathway during tachycardia was shorter than the refractory period in Patient 1 (300 msec in Patient 2 and 350 msec in Patient 1).

With appropriately timed double ventricular premature stimuli delivered either during tachycardia or during regular ventricular pacing, two different sequences of retrograde atrial activation could be identified. In Figure 2 (panel A) two ventricular premature stimuli are delivered during tachycardia, the first at a coupling interval previously shown to result in termination of tachycardia by block within the accessory pathway. Then, a second ventricular impulse was delivered starting late in the cycle, and increasing the prematurity of the test impulse in steps of 10 msec. This second ventricular impulse was conducted in retrograde manner to the atrium, revealing: (1) a shorter V-A conduction time than that observed either during tachycardia or after ventricular premature complexes not resulting in termination of the arrhythmia, and (2) a sequence of atrial activation different from that seen during tachycardia or after ventricular premature impulses advancing retrograde atrial activity without terminating tachycardia. This different pattern of retrograde atrial activity never resulted in continuation of tachycardia. Shortening of the premature beat interval of this second

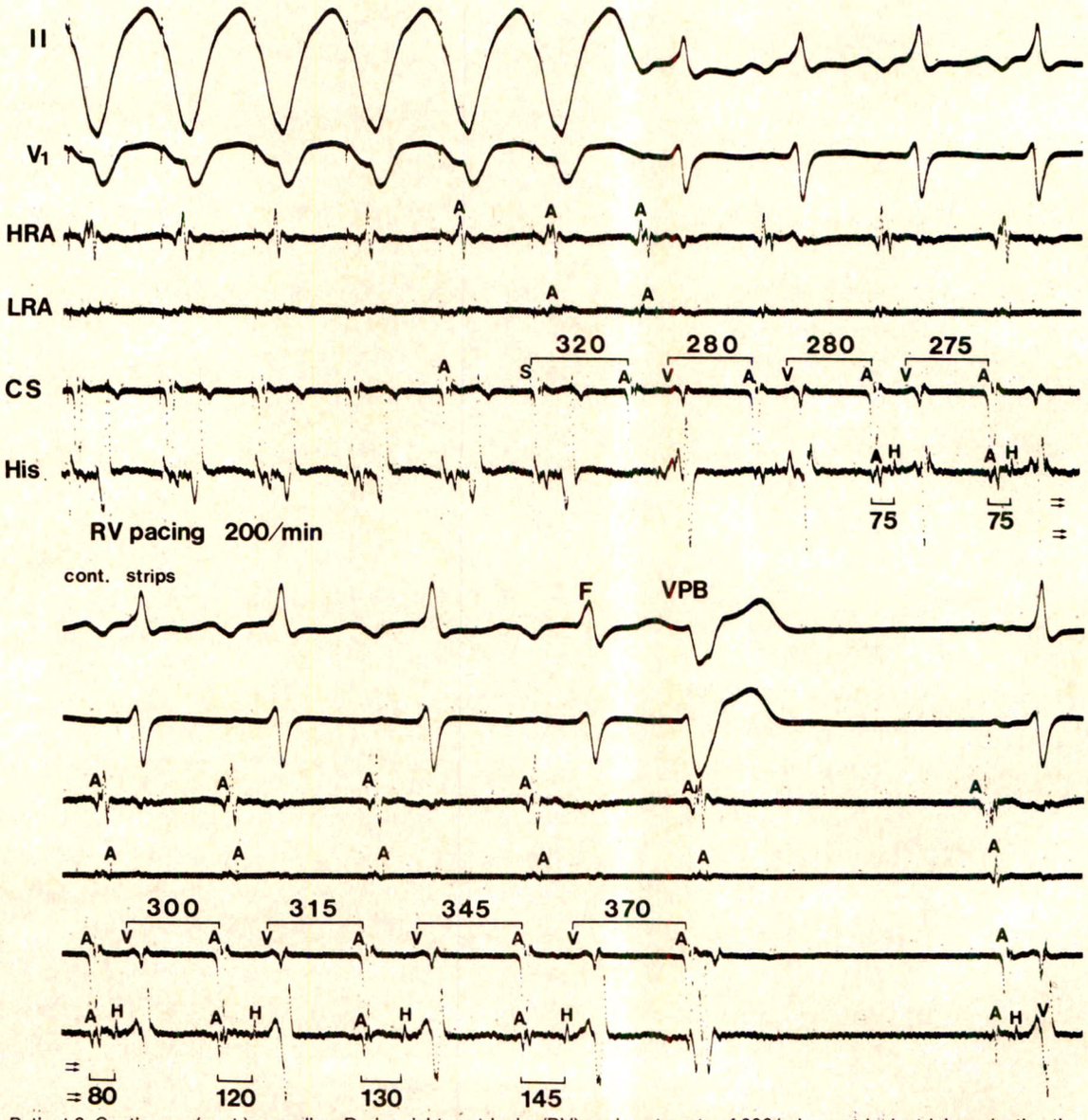

FIGURE 4. Patient 2. Continuous (cont.) recording. During right ventricular (RV) pacing at a rate of 200/min, ventriculoatrial conduction time is shorter than during tachycardia. After cessation of pacing the shortened A-H and V-A time (compare with Fig. 1) gradually lengthen. Tachycardia is terminated by a spontaneously occurring ventricular premature complex (VPB) that is not conducted to the atrium. F = fusion heat between a tachycardia QRS complex and a ventricular premature complex; other abbreviations as in Figure 1.

ventricular stimulus resulted in sudden lengthening of V-A time with a sequence of retrograde atrial activation identical to that observed during tachycardia (Fig. 2, panel B). This pattern resulted in reinitiation of tachycardia.

Observations during ventricular pacing at increasing rates: In Patient 1 regular ventricular pacing at increasing rates resulted in Wenckebach V-A conduction over the accessory pathway followed by V-A block and a few beats showing V-A conduction over the A-V node at a pacing rate of 150/min (Fig. 3). In Patient 2 ventricular pacing at increasing rates resulted in V-A block and V-A dissociation at a rate of 190/min. Slower ventricular paced rates revealed in this patient V-A conduction over the accessory pathway. On maintaining a ventricular pacing rate of 190/min, two sequences of retrograde atrial activation could be demonstrated (similar to the sequences shown in Figure 3). This was followed by 1:1 V-A conduction over the accessory pathway, which was maintained at a ventricular pacing rate of 200/min. V-A time by way of the accessory pathway was then significantly shorter than before this fast pacing rate (Fig. 4). Tachycardia continued after ventricular pacing was stopped, and the A-H and V-A times became shorter then those recorded before pacing. As illustrated in the lower panel of Figure 4 (which is continuous with the upper panel), with tachycardia there was progressive lengthening of the R-R interval up to the termination of tachycardia by a spontaneous ventricular premature complex. Lengthening of the R-R interval was found to be based on lengthening of both the V-A and A-H intervals.

Effects of atrial premature beats during tachycardia: Atrial premature stimuli were introduced during tachycardia from the high right atrium and the coronary sinus. In both patients single or double atrial premature stimuli, or both, resulted in lengthening of the A-H interval.

The following observations were made during this mode of stimulation:

1. Single high right atrial premature stimuli delivered late in the tachycardia cycle without affecting the coronary sinus atrial electrogram nevertheless advanced the timing of the His

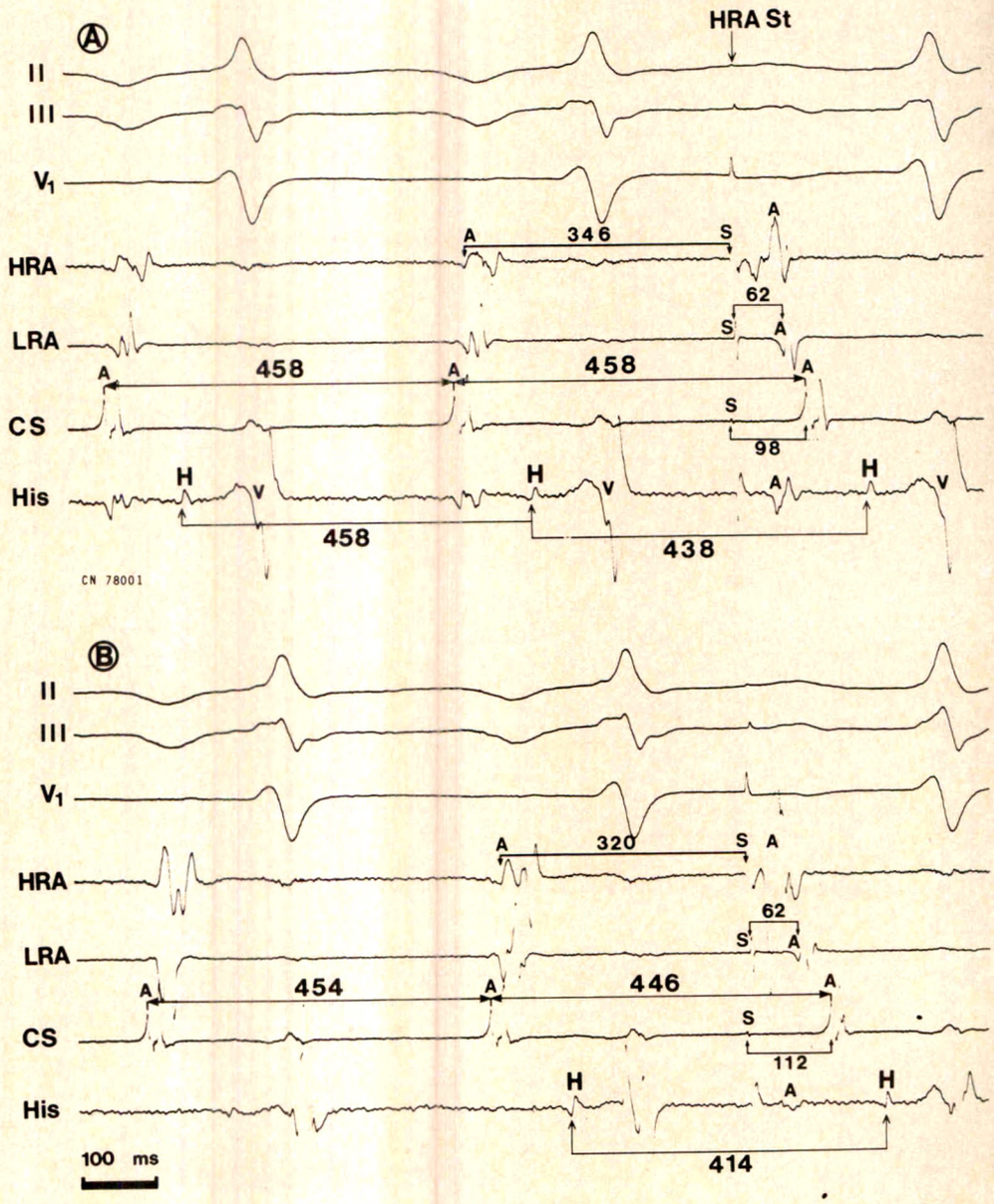

FIGURE 5. Patient 2. **A,** capture of the ventricle during tachycardia by a high right atrial premature stimulus (HRA St) does not influence the timing of activation of the atrial electrogram in the coronary sinus (CS) lead. This finding excludes an upper common pathway in the atrioventricular node during tachycardia. **B,** a right atrial premature stimulus (S) given 26 msec earlier captures not only the ventricule but also the atrium at the site of the coronary sinus recording. This recording was made at a paper speed of 250 mm/sec. Abbreviations as in Figures 1 and 2.

bundle activation, thus excluding an upper common pathway within the A-V node (Fig. 5).

2. Tachycardia could be terminated by single (Patient 1) or double (Patient 2) high right atrial premature stimuli whenever block in the A-V node occurred.

3. In Patient 2, a block in the A-V node could be achieved after the second of two consecutive coronary sinus atrial premature stimuli without termination of tachycardia. When this phenomenon occurred (Fig. 6) a second atrial activity with a sequence identical to that during tachycardia was observed. This atrial activity was the result of V-A conduction over the accessory pathway of the ventricular complex that followed the first of the two atrial premature beats. A critical prematurity of the second atrial stimulus was needed before this phenomenon was manifested. This observation, which was not made after double high right atrial extrastimuli produces evidence against the existence of an intranodal upper common pathway and suggests that atrial refractoriness in the coronary

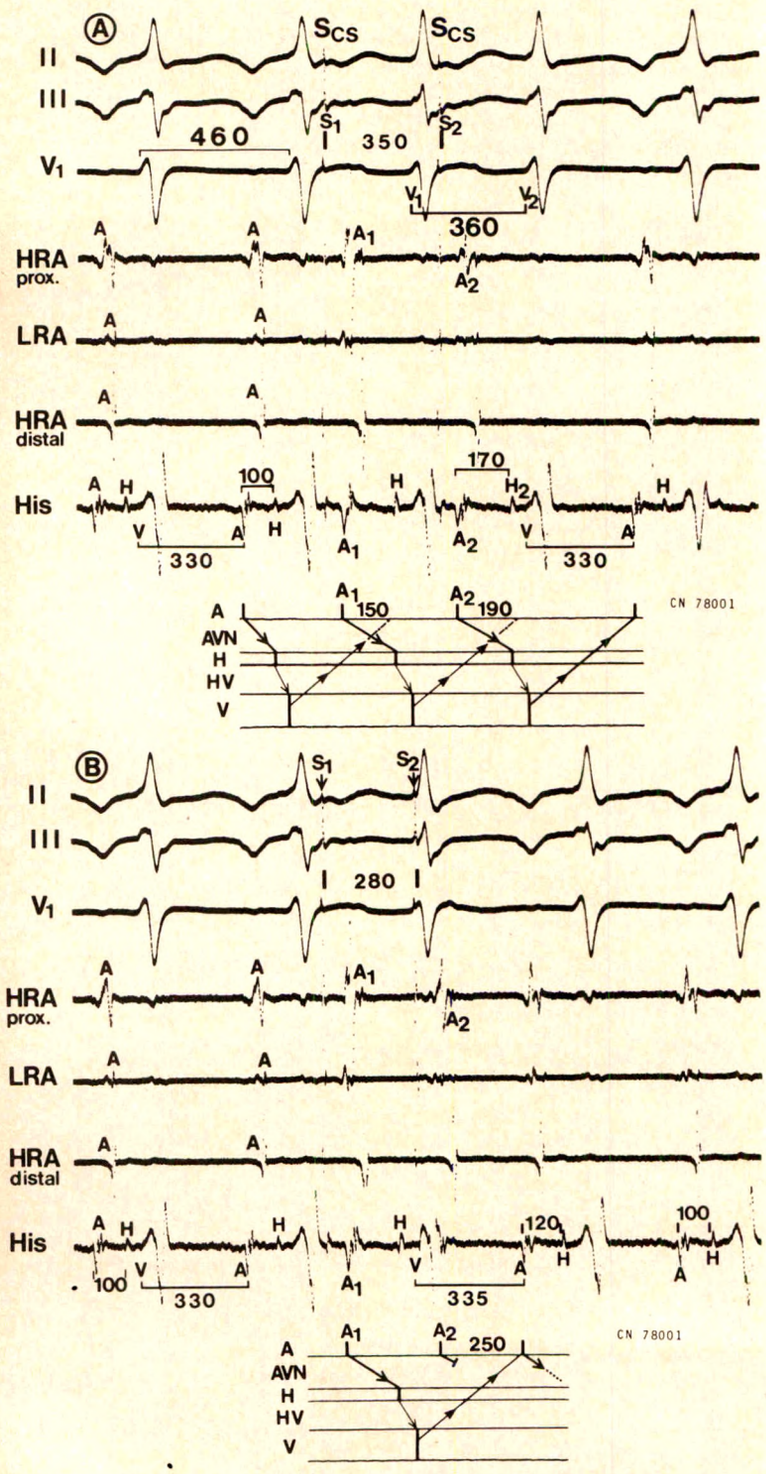

FIGURE 6. Patient 2. **Upper panel,** two consecutive atrial premature stimuli given in the coronary sinus (S_{cs}) are both conducted to the ventricle (V_1 and V_2) without terminating tachycardia. Note that both show prolongation of the A-H interval (**ladder diagram**). **Lower panel,** when the second premature stimulus (S_2) is advanced by 70 msec, block occurs in the atrioventricular node (AVN). This second atrial premature impulse is at the atrial level and is shortly thereafter followed by retrograde atrial activity after the QRS complex resulting from the first atrial premature impulse (**lower ladder diagram**). In this record leads II, III, V_1, two high right atrial leads (HRA prox and HRA dist), a low right atrial lead (LRA) and a His bundle lead (HIS) were recorded simultaneously.

sinus area was responsible for the findings shown in panel A of the Figure 6. The demonstration of retrograde atrial activity as an essential requirement for continuation of tachycardia supports the evidence for an upper common pathway located at the atrial level.

4. In both patients after single atrial premature stimuli the H-H and R-R intervals could be advanced by more than 100 msec (120 msec in the example of panel A of Figure 7) during tachycardia. Despite this, the V-A time after the advanced ventricular complex remained constant.

Effect of atrial pacing at increasing rates: Atrial pacing at increasing rates was performed only in Patient 1. At rates of 200 beats/min 1:1 A-V conduction was observed during high right atrial and coronary sinus stimulation. The A-H interval increased during high right atrial stimulation from 75 msec at an atrial pacing rate of 150/min to 100 msec at a pacing rate of 200/min.

Effect of bundle branch block during tachycardia: In Patient 1, single atrial extrastimuli during tachycardia given with sufficient prematurity were conducted to the ventricle with either right or left bundle branch block aberrancy. Tachycardia continued after this aberrantly conducted complex. V-A time after these aberrant QRS complexes was identical to that measured after normally conducted complexes. This observation provides evidence for a septal location of the accessory pathway.[14] In addition, it suggests that the accessory pathway is independent of the infra-Hisian fascicular system because the V-A time after these aberrantly conducted complexes remained constant despite different degrees of prolongation in H-V time.

Effect of ajmaline: In Patient 1 the intravenous administration of 25 mg of ajmaline (0.75 mg/kg body weight) did not appreciably influence the tachycardia. The tachycardia cycle length was prolonged by 20 msec (440 before versus 460 msec after drug administration). This change was due to a 10 msec lengthening of both the H-V time and the A-H interval, the V-A conduction time remaining constant (340 msec) despite a 10 msec increase in the QRS width.

Effect of atropine: In Patient 1 the administration of 0.5 mg of atropine intravenously resulted in significant acceleration of the tachycardia with a corresponding abbreviation in both the V-A time and the A-H interval (Fig. 8). The increase in rate of tachycardia was mainly due to shortening of the V-A time over the accessory pathway.

Effect of exercise: Exercise resulted in acceleration of tachycardia, from 140 to 190 beats/min in Patient 1, and from 130 to 170 beats/min in Patient 2. Exercise testing was performed outside the cardiac laboratory so that no intracavitary

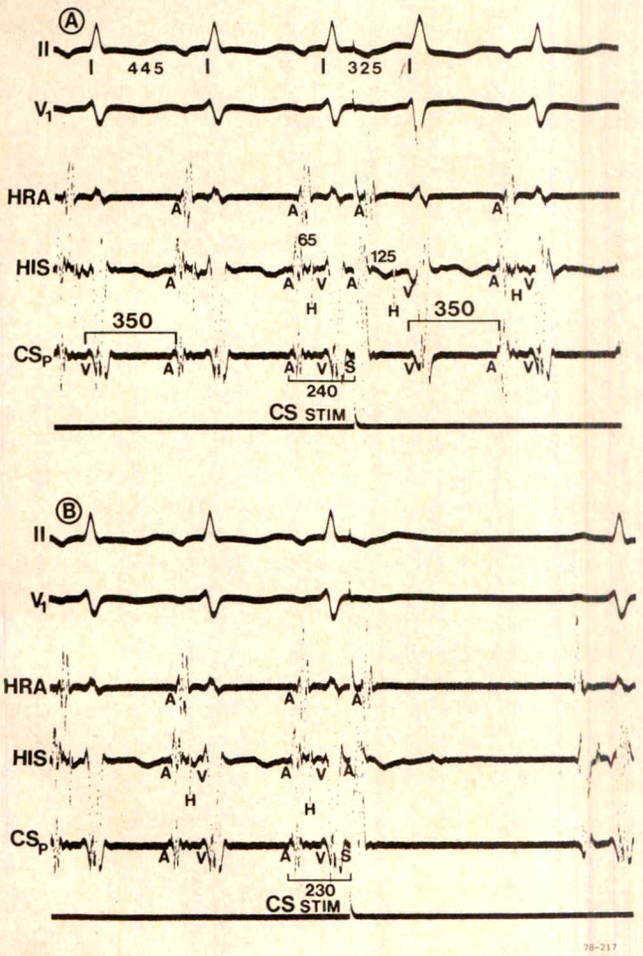

FIGURE 7. Patient 1. **A,** an atrial premature stimulus given after 240 msec in the coronary sinus (CS STIM) advances the next QRS complex of the tachycardia by 120 msec. The A-H interval increases to 125 msec from a duration of 65 msec during tachycardia. The ventriculoatrial interval does not change after the premature activation of the ventricle. **B,** termination of tachycardia by an atrial premature stimulus given 10 msec earlier, which is blocked in the atrioventricular node. S = stimulus; other abbreviations as in Figures 1 and 2.

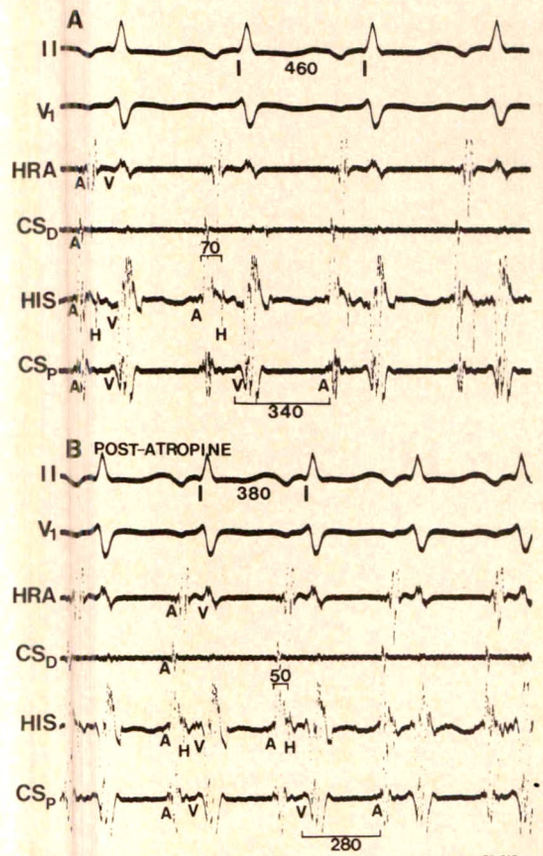

FIGURE 8. Patient 1. Effect of atropine on the tachycardia. Comparison of panels **A** (before atropine) and **B** (after atropine) reveals shortening of the A-H interval by 20 msec and of the V-A interval by 60 msec. Abbreviations as in Figures 1 and 2.

documentation is available. From the surface electrocardiogram it could be demonstrated that this exercise-induced acceleration of the tachycardia was mainly due to shortening of the R-P interval, that is, reduction of the conduction time by way of the accessory pathway.

Spontaneous termination of tachycardia: Several spontaneous terminations of tachycardia were observed in both patients. Spontaneous termination of tachycardia was preceded by a V-A prolongation with corresponding lengthening of the R-R interval. The tachycardia cycle length immediately before spontaneous termination was longer than the cycle length after spontaneous initiation because of a longer V-A time.

Patient 3

Pseudoventricular A-V junctional circus movement tachycardia: Patient 3 had a tachycardia with wide QRS complexes (Table I) that was thought to be ventricular in origin before the electrophysiologic investigation. Intracavitary recordings during tachycardia demonstrated 1:1 V-A conduction by way of the His–A-V nodal axis (Fig. 9). During sinus rhythm, no preexcitation was present. The P-A time measured 40 msec, the A-H interval 50 msec and the H-V time 50 msec.

Modes of initiation of tachycardia: *Tachycardia could be induced during the stimulation study in the following way:*

1. After single atrial premature stimuli A-V conduction occurred over the A-V node showing a gradual increase in A-H time without change in H-V time or QRS configuration up to an atrial premature stimulus interval of 290 msec; block then occurred in the A-V node. On further shortening of the premature stimulus interval (Fig. 9), an atrial extrastimulus given during a regular atrial paced rhythm (basic cycle length 500 msec) is blocked above the bundle of His but followed by the initiation of tachycardia showing wide QRS complexes. This phenomenon was reproducible from an atrial premature stimulus interval of 290 msec to the refractory period of the right atrium (250 msec). The interval between the atrial premature stimulus to the first QRS complex of the tachycardia increased from 500 msec, after an atrial premature stimulus interval of 290 msec, to 550 msec after an atrial premature stimulus given after 250 msec.

2. After single ventricular premature stimuli during a regular ventricular paced rhythm (basic cycle length 600 msec) in a zone of premature stimulus intervals ranging from 360 msec to the effective refractory period of the right ventricle (250 msec), V-A conduction of all ventricular premature stimuli occurred over the normal His–A-V nodal pathway up to the refractory period of the right ventricle. Although an inverse relation was found between the prematurity of the tachycardia-inducing ventricular impulse and the interval between this extrastimulus and the first tachycardia beat (Fig. 10), the distance between the atrial electrogram in the His lead after the ventricular test stimulus and the first beat of the tachycardia remained practically constant.

Mode of termination of tachycardia: The tachycardia could reproducibly be terminated by (1) an atrial premature paced stimulus that was not conducted to the ventricle (Fig. 9), and (2) two consecutively given ventricular stimuli; termination could be accomplished with the latter only if the second ventricular premature stimulus was blocked in a retrograde manner in the A-V node.

Effect of atrial impulses during tachycardia: Random atrial pacing during tachycardia resulted in occasional atrial captures. Some of these atrial impulses influenced the tachycardia cycle, which was shortened by as much as 35 msec. These advanced ventricular complexes were not fusion complexes because no change in QRS configuration was observed and no His potential preceded them.

Discussion

Previous studies on accessory retrograde pathways with long conduction times: Epicardial excitation mapping, intracardiac electrophysiologic studies and the outcome of surgical interventions proved the presence of accessory A-V connections. Anatomic evidence of the existence of these accessory pathways is also available.[15] Conduction times over these accessory A-V pathways are shorter than conduction times over the A-V nodal–His pathway, in both the anterograde and retrograde directions. This explains the presence of ventricular preexcitation in the Wolff-Parkinson-White syndrome[16] and the finding of a V-A time shorter than the A-V time during a reciprocating tachycardia utilizing the accessory pathway in the V-A direction.[17]

Coumel et al.[13] reported on a form of junctional reciprocating tachycardia characterized by a V-A time longer than the A-V interval in which a single ventricular premature stimulus delivered during tachycardia could advance atrial activity at a time when the His bundle was refractory. They believed that either a Mahaim (nodoventricular) fiber or longitudinal dissociation in the bundle of His could explain this finding. They considered the upper pathway of this reentry circuit to be located within the A-V node because the retrograde limb of the reentry loop showed a very long conduction time (leading to a P-R interval shorter than

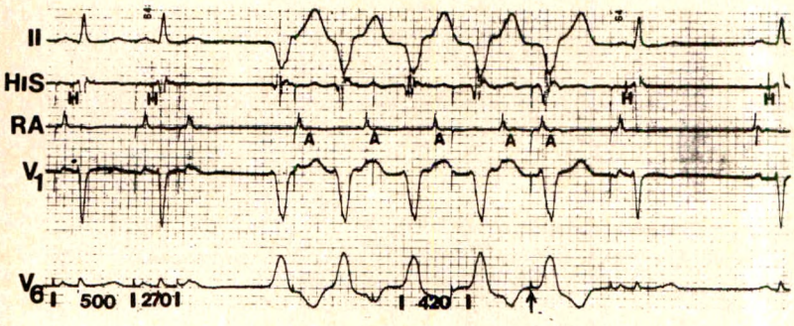

FIGURE 9. Patient 3. Initiation and termination of tachycardia during atrial pacing. Tachycardia is initiated after an atrial premature stimulus given after 270 msec during regular pacing of the atrium with a basic cycle length of 500 msec. This stimulus is blocked in the A-V node but is followed after 540 msec by a tachycardia with wide QRS complexes (QRS width 140 msec) and no His bundle activation preceding the QRS complex. Atrial pacing was continued during tachycardia. RA = right atrium; other abbreviations as in Figure 1.

the R-P interval) and decremental conducting properties.[13]

Gallagher and Sealy[18] recently reported on a patient with the clinical and electrocardiographic characteristics of the permanent form of the junctional reciprocating tachycardias in whom endocardial and epicardial mapping studies were performed. During these studies they demonstrated that this tachycardia was indeed based on a junctional reentry mechanism, the retrograde limb of the circuit being an accessory A-V pathway despite the very long conduction times leading to a V-A interval longer than the A-V time.

Two different sequences of retrograde atrial activation were demonstrated, one through the accessory pathway and the other by way of the normal His–A-V nodal pathway. In addition, after the surgical creation of complete anterograde A-V block, V-A conduction persisted with R-P intervals of 270 msec, similar to those intervals measured before the intervention. Gallagher and Sealy concluded that an accessory A-V connection revealing signs of decremental conduction (gradual prolongation of V-A times with increasing prematurity of ventricular test stimuli) was incorporated in the tachycardia circuit, and they postulated that this anomalous pathway could be an accessory A-V nodal structure.

Features of Patients 1 and 2: Our Patients 1 and 2 had findings similar to those of patients described by Coumel[13] and Gallagher.[18] An atrial origin of the tachycardia could be excluded because (1) ventricular premature stimuli given during tachycardia advanced atrial activation with a sequence of atrial activation identical to that during tachycardia, and (2) critically timed ventricular premature stimuli could reproducibly terminate tachycardia whenever block occurred in V-A conduction. These observations indicate that the mechanism of termination of tachycardia was by way of the block in the retrograde limb of a junctional reentry circuit (Fig. 1 and 2). That the retrograde arm of the reentry loop consisted of an accessory pathway that bypassed the bundle of His was demonstrated by giving ventricular premature stimuli during the tachycardia, which advanced atrial activity at a time when the His bundle was refractory (Fig. 1B and 2A).

As in the case reported by Gallagher and Sealy,[18] our patients manifested two different sequences of retrograde atrial activation (Fig. 2B and 3). This finding excludes longitudinal dissociation of the bundle of His as the mechanism of the tachycardia. In addition, the existence of two different atrial exits for the A-V node and the accessory pathway argues against a nodoventricular (Mahaim) tract and suggest the presence of an

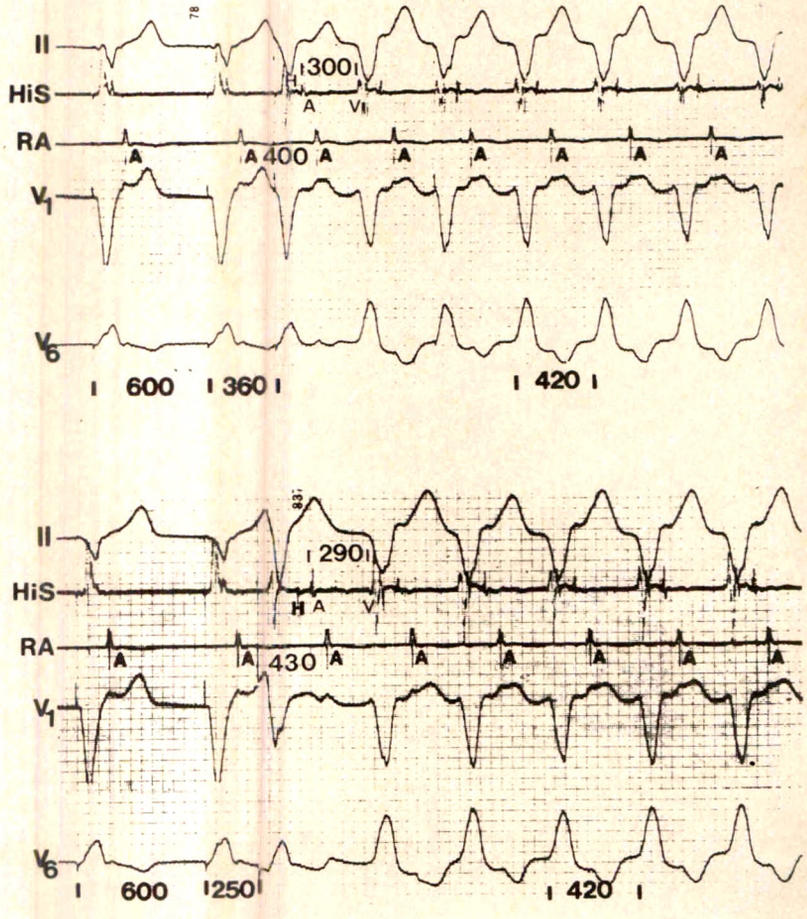

FIGURE 10. Patient 3. Initiation of tachycardia by a ventricular premature stimulus during right ventricular pacing with a basic cycle length of 600 msec. All premature impulses given within an interval range of 360 msec (**upper panel**) to the refractory period of the right ventricle (250 msec) (**lower panel**) were followed by tachycardia. After the ventricular premature impulse and during tachycardia ventriculoatrial conduction occurs by way of the atrioventricular node. Abbreviations as in Figures 1 and 9.

A-V anomalous pathway. Although different sites of entrance from the atrium into the A-V node have been described in experimental animal preparations, two different sites of A-V nodal exit into the atrium during V-A conduction have not been demonstrated.[19]

The following previously unreported observations provide further supportive evidence for an intraatrial upper common pathway during the tachycardia:

1. Single high right atrial premature stimuli delivered late in the tachycardia cycle were able to advance activation of the bundle of His at a time when the coronary sinus atrial electrogram resulting from V-A conduction of the preceding tachycardia beat was not affected (Fig. 5).

2. The second of two appropriately timed coronary sinus atrial premature stimuli could be blocked in the A-V node without affecting V-A conduction of the preceding conducted beat (Fig. 6). This observation makes an upper common pathway without the A-V node very unlikely because the V-A time of the ventricular complex resulting from the first atrial premature impulse remained practically unchanged (5 msec longer) even though the second (intranodally blocked) atrial premature impulse had penetrated the A-V node to some extent. The occurrence of the latter event is supported by the observation that the A-V interval at reinitiation of the tachycardia was 20 msec longer than the interval during subsequent tachycardia cycles. That atrial refractoriness (as postulated in Fig. 6) was the limiting factor preventing the manifestation of this phenomenon at longer premature beat intervals of the second coronary sinus test impulse is suggested by the fact that double high right atrial premature stimuli did not permit this observation even though block was induced in the A-V node.

The sequence of retrograde atrial activation during tachycardia in these two patients supports a septal location of the accessory pathway.[20] In addition, the observation in Patient 1 that left and right aberrantly conducted beats during tachycardia did not result in V-A prolongation further supports a septal location of this accessory pathway.[14]

The observation made in Patient 2, that a single right apical ventricular premature impulse delivered late in the tachycardia cycle could advance the subsequent atrial activity by 25 msec without advancing the ventricular electrogram in the His bundle lead, was previously made by Coumel et al.[13] in one of their patients with a similar type of tachycardia. In addition, they demonstrated that ventricular premature stimuli during tachycardia could more easily capture the atrium when delivered from the right ventricular apex than when delivered from the right ventricular septum. Coumel et al. suggested that the accessory pathway was "electrophysiologically" closer to the right ventricular apex than to the right ventricular septum. These observations combined with the previous arguments for a septal location of the accessory pathway are compatible with the possibility of an anatomically long accessory pathway in these patients.

Features in Patient 3: The type of tachycardia observed in Patient 3 has not previously been described. Its reproducible mode of initiation after atrial premature stimuli that are not conducted to the bundle of His rules out a ventricular origin. Also the shortening of the R-R interval and termination of the tachycardia by atrial premature stimuli not conducted over the bundle of His argue against a ventricular origin.

The initiation of a "ventricular-like" tachycardia after atrial premature impulses that are blocked within the A-V node has previously been observed in patients with the Wolff-Parkinson-White syndrome, in the so-called antidromic reciprocating tachycardia during which the accessory pathway is used in the A-V direction. However, atrioventricular conduction times in these patients are characteristically short, whereas in Patient 3 the interval between the low septal right atrial electrogram (atrial signal in the His bundle lead) and the beginning of the subsequent ventricular activity was 300 msec. Therefore, in this patient as in the two previously discussed, an accessory pathway with long conduction time seems to be incorporated in the reentry circuit. The QRS-configuration during tachyardia and during right apical ventricular pacing looked similar (Fig. 9), suggesting that the ventricular end of the accessory pathway is located near the right ventricular apex. The fact that a "ventricular-like" tachycardia can be influenced and terminated by atrial impulses that are not conducted to the bundle of His or to the ventricles over the normal A-V pathway indicates that structures situated above the bundle of His are required to sustain the arrhythmia. Such a tachycardia therefore is not of ventricular origin and is more likely based on a junctional reciprocating mechanism.

The reentry circuit seems to be composed of the following structures: (1) an anterograde conducting accessory pathway with a long conduction time, (2) ventricular myocardium, and (3) the His–A-V nodal pathway. Although one would tend to postulate an atrioventricular accessory pathway, a Mahaim (nodoventricular) tract cannot be excluded. Under both circumstances either the true A-V pathway or the nodoventricular connection must have a very long conduction time (approximately 300 msec).

Nature of the accessory pathways participating in these tachycardias: In these three patients a junctional reciprocating tachycardia utilizing an accessory pathway characterized by very long conduction times was demonstrated. In the tachycardia reported by Gallagher and Sealy[18] an accessory A-V nodal structure was postulated to explain the long conduction times and the phenomenon of increase in V-A time after induced ventricular premature complexes, suggesting decremental conduction over the accessory pathway. This feature was also found in our Patients 1 and 2. We also found shortening of V-A times after administration of atropine (Patient 1) and often after exercise (both patients). Even a Wenckebach sequence during V-A conduction by way of the accessory pathway could be demonstrated in both patients. All these findings support the hypothesis that the accessory pathway has A-V nodal properties.

If the cause for slow conduction were aberrant A-V nodal tissue, one would expect this tissue to be located

in the A-V ring, close to the septum. However, as observed by Coumel and also by us in our Patient 2 (Fig. 1A), ventricular premature stimuli delivered at the right ventricular apex could advance retrograde atrial activity without affecting the ventricular electrogram of the His bundle lead. This finding suggests that the ventricular end of the accessory pathway is situated rather far from the A-V ring. We conclude that accessory pathways with long conduction times, either because of a long intracardiac pathway or slow conducting properties, or both, exist in the human heart and may be involved in reciprocating tachycardia.

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The Risk of Pericardiocentesis

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The risk and potential risk factors of pericardiocentesis were assessed by a review of a series of 52 pericardiocenteses comprising all those performed in the cardiac catheterization laboratory of one institution from 1971 to 1978. On the basis of the operative results, the patients were separated into two groups for comparison: Group I comprised all patients with a successful uncomplicated (35) pericardiocentesis and Group II all those with a nonproductive (16), nontherapeutic (1) or complicated (8) pericardiocentesis. Complications consisted of one death, one cardiac arrest, one aspiration of a subdiaphragmatic abscess and five ventricular punctures without adverse sequelae. Among the patients who had a nonproductive pericardiocentesis, the condition of 11 had probably been misdiagnosed but at least 4 had a false negative pericardiocentesis. Comparison of the two groups showed no significant difference in the incidence of cardiac tamponade or in the clinical presentation based on historical, physical, electrocardiographic, roentgenographic or echocardiographic findings of pericardial disease. Pericardiocentesis was usually successful when performed for suspected malignant pericardial effusion but often unsuccessful when performed for suspected hemopericardium. Anatomically, all patients in Group II had either minimal or loculated posterior pericardial effusion. It is concluded that pericardiocentesis can be performed at a low risk that can be further minimized by consideration of the disease process and the anatomic location of the pericardial fluid.

Pericardiocentesis, a method successfully used since 1840,[1] is dramatic and life-saving when performed to relieve cardiac tamponade. However, serious complications, including death, can occur. Some physicians believe that pericardiocentesis should not be performed routinely unless cardiac tamponade is present,[2–4] and they recommend direct surgical drainage of the pericardial sac,[4,5] but unfortunately this procedure can also result in significant complications.[6] We carried out this study to reassess the risk of pericardiocentesis, with particular emphasis on identifying factors that could lead to improved selection of patients and minimize the hazards.

Methods

Selection and classification of patients: The records of all patients who underwent pericardiocentesis in our cardiac catheterization laboratory in a 6 year period (July 1, 1972 to July 1, 1978) were reviewed to determine the clinical presentation, the pericardiocentesis procedure, the results of pericardiocentesis and the subsequent course of the patients.

The clinical presentation of each patient before pericardiocentesis was analyzed to determine which clinical findings of pericardial disease were present before pericardiocentesis and whether the diagnosis had been pericardial effusion with or without cardiac tamponade. Because of the retrospective nature of the study, no attempt was made to quantitate the degree of cardiac compromise,

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the rapidity with which it developed or the extent to which constrictive pericarditis complicated cardiac tamponade. The specific clinical features assessed were the symptoms of chest pain and dyspnea; the physical findings of pulsus paradoxus (greater than 10 mm Hg decrease in systolic pressure on inspiration), jugular venous distension and pericardial friction rub; the electrocardiographic findings of arrhythmias, low voltage (QRS complex less than or equal to 5 mv in the limb leads or less than 10 mv in the precordial leads) and total electric alternans of the P, QRS and T waves; the roentgenographic findings of a positive epicardial fat pad sign[7,8]; and the echocardiographic finding of an echo-free space between the pericardium and the myocardium by the criteria of Feigenbaum.[9]

The pericardiocenteses were analyzed to determine the number of procedures that were successful, nonproductive, nontherapeutic or complicated. A pericardiocentesis was considered successful if pericardial fluid adequate for diagnostic analysis was obtained and if cardiac tamponade, when present, was relieved. Relief of cardiac tamponade was defined by the alleviation of pulsus paradoxus or venous hypertension by removal of pericardial fluid. Constrictive pericarditis was defined by the relief of clinical signs of cardiac constriction by removal of the pericardium. The successful pericardiocenteses were reviewed to determine how many provided a positive pathologic diagnosis. The subsequent course of the patients with a nonproductive pericardiocentesis was assessed to determine the number with subsequently documented pericardial effusion and cardiac tamponade (false negative pericardiocentesis) and the number with no significant pericardial effusion (misdiagnosis).

On the basis of the results of pericardiocentesis, the patients were classified into two groups: Group I comprised all patients with an uncomplicated successful pericardiocentesis, and Group II all patients with a nonproductive, nontherapeutic or complicated pericardiocentesis. The two groups were compared to determine if there was any significant difference in the clinical presentation. Statistical analysis was made with the chi square method. Because repeated statistical analysis may produce spurious findings, the significant level α for the chi square test was obtained from the upper percentage points of the Bonferroni chi square statistic. With use of the Bonferroni tables, several hypotheses on categorical data can be tested simultaneously regardless of correlations among the test statistics, and the nominal α level is preserved.[10]

All pericardiocenteses were performed in the cardiac catheterization laboratory with fluoroscopic and electrocardiographic monitoring, using the anterior subxiphoid approach. All were performed by a cardiology trainee with an attending cardiology staff physician; at least five different attending cardiologists were involved with these procedures. In our institution, pericardiocentesis is routinely performed in the cardiac catheterization laboratory and rarely done "blindly" at the bedside.

Patients: Fifty-two pericardiocenteses were performed in 49 patients (22 women and 27 men). Three patients had two separate pericardiocenteses. The mean age of the patients was 49 years (range 16 to 95). Thirty-five patients had clinical signs of cardiac tamponade and underwent diagnostic/therapeutic pericardiocentesis. Seventeen patients presented without clinical evidence of cardiac tamponade and underwent diagnostic pericardiocentesis. The clinical diagnoses of the patients are shown in Table I. In addition to the specific diseases listed, there was a variety of associated diseases (listed under miscellaneous) including myxedema, ulcerative colitis, systemic lupus erythematosus, acute pancreatitis and congestive heart failure. Some patients had no associated disease and were presumed to have viral pericardial effusion.

Results

Results of pericardiocenteses (Table I): In Group I (35 procedures), cytologic examination of the pericardial fluid provided a positive diagnosis in 75 percent of the patients with suspected malignant pericardial effusion; culture of the pericardial fluid provided a positive diagnosis in 25 percent of the patients with suspected tuberculosis; and inspection of the pericardial fluid provided a positive diagnosis in 50 percent of the patients with hemopericardium.

In Group II (17 procedures), 15 pericardiocenteses were nonproductive, 1 was nontherapeutic and 1 was successful but complicated by right ventricular puncture. There were eight complications: one death, one cardiac arrest with a successful resuscitation, one aspiration of an unsuspected subdiaphragmatic abscess and five right ventricular punctures. All complications except one right ventricular puncture occurred among the patients with a nonproductive pericardiocentesis. Except for the one death, none of the complications caused any adverse sequelae for the patient. The final diagnoses of the 16 patients with a nonproductive or nontherapeutic pericardiocentesis (Table II) were based on medical follow-up (8 patients), subsequent pericardiectomy-pericardiotomy performed (6 patients) and postmortem examination performed within a week of pericardiocentesis (2 patients). Eleven patients had no significant pericardial effusion. The absence of a significant amount of pericardial fluid was confirmed by pericardiectomy or postmortem examination in five patients. One patient had uremic constrictive pericarditis with a small amount of pericardial effusion aspi-

TABLE I

Pericardiocentesis: Etiology and Results

Diseases	no. of PC	Group I*	Group II*	Complications
Malignant	21	19(15D)	2(1FN)	1 aspiration of unsuspected abscess
Hemopericardium	6	2	4(2FN)	
Uremia	5	3	2	
Tuberculosis	4	3(1D)	1	1 right ventricular puncture
Miscellaneous	16	8	8	4 right ventricular punctures, 1 cardiac arrest, 1 death
Total	52	35(16D)	17	

* Group I = uncomplicated and productive pericardiocentesis; Group II = complicated, nonproductive or nontherapeutic pericardiocentesis.
CA = cardiac arrest; D = pericardiocenteses that provided a positive diagnosis; FN = false negative pericardiocenteses; PC = pericardiocenteses.

TABLE II

Nonproductive Pericardiocentesis: Follow-Up Diagnosis

No significant pericardial effusion	11 (5)*
Congestive heart failure	6
Uremic pericarditis	1
Fibrinous pericarditis	2
Cardiomegaly (unexplained)	1
Tumor encasement of the heart	1
Pericardial effusion	5 (4)*
Uremic constrictive pericarditis	1
Fibrinous pericarditis	1
Loculated hemopericardium	2
Loculated malignant effusion	1

* Documented at pericardiectomy or postmortem examination.

rated without relief of cardiac constriction which required pericardiectomy.

There were four false negative pericardiocenteses: One patient with fibrinous pericarditis had 200 ml of pericardial fluid found at pericardiectomy; three patients had true cardiac tamponade, including two who had a loculated posterior hemopericardium removed at pericardiectomy with relief of cardiac tamponade. The third patient had a previously diagnosed malignant pericardial effusion with clinical signs of cardiac tamponade and presumed loculated pericardial effusion. Because of her condition, pericardiectomy was not performed after pericardiocentesis, and she died a week later. The patient who died during pericardiocentesis presented in a moribund state with severe heart failure and cardiogenic shock. On postmortem examination, he was found to have severe arteriosclerotic heart disease.

The annual incidence of complications or of nonproductive, nontherapeutic pericardiocenteses decreased during the 6 year period. There were no deaths or cardiac arrests in the last 5 years, and the incidence of complications in the last 3 years (25 percent) was less than in the first 3 years (48 percent).

Clinical presentation: Table III compares the clinical findings in the patients in Group I and Group II. The diagnosis of cardiac tamponade was not associated with a lesser incidence of nonproductive or complicated pericardiocentesis. There was no significant difference between the two groups in the symptoms and physical findings. Neither the prepericardiocentesis diagnosis of cardiac tamponade nor the presence of pulsus paradoxus was predictive of the risk of pericardiocentesis.

Chest roentgenograms: Thirty-four chest roentgenograms taken within 1 week of pericardiocentesis were available for review (31 frontal and lateral views and 3 portable frontal views.) The epicardial fat pad sign was present in 15 patients (42 percent): 4 in the frontal view only, 10 in the lateral view only and 1 in both the frontal and lateral views. All patients with a positive pericardial fat pad sign had pericardial disease, but not all had pericardial fluid. There was no significant difference between the two groups in the frequency of this sign in the chest roentgenogram.

Electrocardiograms: Forty-nine electrocardiograms taken within 48 hours before pericardiocentesis were

TABLE III

Pericardiocentesis: Clinical Findings

	Group I	Group II	*P* Value
Prepericardiocentesis diagnosis			
No cardiac tamponade	10	7	NS
Cardiac tamponade	25	10	NS
Clinical findings			
Dyspnea	23	10	NS
Chest pain	8	5	NS
Jugular venous distension	23	9	NS
Pulsus paradoxus	19	5	NS
Pericardial friction rub	6	7	NS
Chest roentgenograms	27	7	
Cardiomegaly	27	7	NS
Epicardial fat pad sign	12	3	NS
Electrocardiograms	32	17	
Low voltage	10	1	NS
Electric alternans	5	0	NS
Sinus rhythm	28	8	NS
Atrial fibrillation/flutter	3	7	NS
Echocardiograms	23	9	NS
Positive	23	8	NS
Equivocal	0	1	NS
"Swinging heart"	5	0	NS

NS = not significant; *P* = probability.

available for direct review. There was no significant difference between Groups I and II in the incidence of supraventricular arrhythmias or low voltage of the QRS complex. Electric alternans of the QRS complex occurred only in patients in Group I, but the incidence was not statistically significant.

Echocardiograms: Thirty-two echocardiograms were available for direct review. Five echocardiograms demonstrated a "swinging heart" in patients who had cardiac tamponade and uncomplicated pericardiocentesis, but this finding was not significant statistically. Of the eight patients in Group II with a positive echocardiogram, three had cardiac tamponade due to loculated effusion, four had pericarditis with a small amount of pericardial effusion and one had tumor encasement of the heart without pericardial fluid; thus, only one echocardiogram was false positive for pericardial effusion. There was no significant difference between the two groups in the incidence of positive echocardiograms.

Discussion

Few studies have attempted to quantify the risk of pericardiocentesis. In 1951, Kotte and Maguire[11] reported that 18 of 21 physicians had seen at least one fatality due to pericardiocentesis, but the incidence of complications was not known. There have been six subsequent reports on the risk of pericardiocentesis[3,4,6,12–14] (Table IV). Comparison of our study with previous studies is difficult because of differences in methodology, duration of study and follow-up assessment of patients. Previous investigators generally have not considered a nonproductive, nontherapeutic pericardiocentesis a complication unless adverse effects resulted. For purposes of analysis, we considered such a pericardiocentesis a complication because a procedure with risk was performed in a patient who derived no

TABLE IV

Reported Complications of Pericardiocentesis

Reference (first author)	Date	Pericardiocenteses (no.)	Complications
Bishop[12]	1956	40	Ventricular puncture (6)
Kilpatrick[3]	1965	20	Cardiac chamber puncture (7), death (1), hypotension (3)
Fredriksen[6]	1971	21	Cardiac chamber puncture (3)
Pradham[4]	1976	5	Cardiac tamponade (1)
Silverberg[13]	1977	21	Cardiac arrest (1)
Krikorian[14]	1978	123	Death (5), hemopericardium (5) ventricular tachycardia (1) nonproductive pericardiocentesis (17)

benefit from it. However, to allow comparison of our results with those of other studies, we also classified the risk of pericardiocentesis into the categories of risk of mortality, risk of morbidity and risk of nonproductive, nontherapeutic pericardiocentesis. In our study, virtually all complications occurred in the patients who were judged to have a nonproductive pericardiocentesis.

Incidence of complications: The incidence of adverse complications was relatively small in our study. The only death occurred in a patient who was already near death with severe cardiac failure (other studies[13] have excluded patients in this situation). We attribute the small incidence of complications to two factors: the increasing use of echocardiography as a diagnostic tool and the controlled conditions under which pericardiocentesis was performed. The period of our study spanned the time of rapid development of the use of echocardiography. Use of echocardiography has undoubtedly decreased the number of patients mistakenly diagnosed as having pericardial effusion and resulted in a better selection of patients for pericardiocentesis. Also of importance is the environment in which pericardiocentesis is performed. Previous studies have generally reported the complications of pericardiocentesis without regard to the conditions under which they were performed. In our study, all pericardiocenteses were performed in the cardiac catheterization laboratory rather than at the bedside, a practice that provides several advantages: Fluoroscopy is available and allows identification of the atrioventricular groove and the path of the main right coronary artery so that these can be avoided during pericardiocentesis, and it permits rapid identification of the site of the exploring needle with use of pressure recording and injection of contrast medium. Also, the presence of trained cardiac catheterization laboratory personnel is of invaluable help in the event of a cardiac arrest or a serious arrhythmia.

Clinical features of pericardial disease significantly associated with the success of pericardiocentesis: We were unable to find any such features, partly because of misdiagnosis of pericardial effusion and partly because of false negative or complicated pericardiocenteses in patients with pericardial effusion and cardiac tamponade. Previous investigators have shown that there are virtually no clinical signs pathognomonic of pericardial effusion and cardiac tamponade.[15,16] In our study, the epicardial fat pad sign in the chest roentgenogram was specific for pericardial disease but not for pericardial fluid. The echocardiogram is an excellent tool for diagnosing pericardial effusion but, false positive results can occur as they did in our patient with tumor encasement.[17–19] No complications occurred among the patients whose electrocardiogram revealed total electric alternans of the QRS complex or whose echocardiogram demonstrated a "swinging heart," but these signs occurred too infrequently to be of major clinical value. Our results do not negate the clinical value of these signs in the diagnosis of pericardial effusion and cardiac tamponade, but they do emphasize their limitations.

Factors determining risk of pericardiocentesis: The follow-up information on the patients with a nonproductive or complicated pericardiocenteses provided insight into the factors that may determine the risk of pericardiocentesis. On a clinical basis, two groups of patients were identified in whom the results of pericardiocentesis differed markedly. Pericardiocentesis for suspected malignant pericardial effusion was very effective both diagnostically and therapeutically. This finding is similar to previous data on the effectiveness of pericardiocentesis in patients with malignant pericardial effusion.[20,21] In contrast, pericardiocentesis for possible hemopericardium after open heart surgery was unsuccessful in 50 percent of the patients with true cardiac tamponade. These data are similar to those of Engelman et al.[22] Thus, we recommend pericardiocentesis for patients with suspected malignant pericardial effusion and pericardiotomy-pericardiectomy for patients with suspected cardiac tamponade due to hemopericardium after open heart surgery.

Our results showed that anatomically both the amount and location of pericardial fluid are important factors. Because virtually all complications of pericardiocentesis stem from the exploring needle touching or penetrating the heart, the more fluid there is between the pericardium and the heart, the less likely the chance of a complication. The patients in Group II had minimal or no pericardial fluid (200 ml or less) or had loculated

pericardial effusions. Those with loculated effusions had a posterior pericardial effusion that could not be reached by the anterior subxiphoid approach. On the basis of these results, we recently assessed the value of the echocardiogram for determining the amount and location of pericardial fluid and found that the width of the anterior clear space correlates significantly with the incidence of complications of pericardiocenteses.[23]

Implications: Our study has reported the risk of pericardiocentesis when performed in the era of echocardiography under optimal conditions by experienced operators or trainees under their close supervision usin the subxiphoid approach. The data suggest that the ris of pericardiocentesis can be minimized by selectin patients with particular consideration of the diseas process causing the pericardial effusion and the amoun of the effusion and its location. We conclude that peri cardiocentesis is a diagnostically and therapeuticall useful procedure that can be performed at low risk, an that this risk can be further minimized by proper se lection of patients based on consideration of the diseas process and the preoperative identification of th amount and location of the pericardial fluid.

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In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with oral maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure antinuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; discontinue drug in event of rising titer or clinical symptoms of LE. Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.

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The dislodgment of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in second degree and third degree A-V block, bundle branch block, or severe digitalis intoxication.

Bear in mind when treating ventricular arrhythmias in patients with severe organic heart disease and ventricular tachycardia that complete heart block, which may be difficult to diagnose, may be present. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus ha been reported with oral maintenance procainamid therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure antinuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; in event of rising titer (antinuclear antibody) or clinical symptoms of LE, assess the benefit/risk ratio related to continued procainamide therapy (see boxed Warning). Steroi therapy may be effective if discontinuation of procainamide does not cause remission of symptoms If the syndrome develops in a patient with recurrer life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be use concomitantly with procainamide.

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A syndrome resembling lupus erythematosus ha been reported in patients on oral maintenance therapy (see Precautions). Reactions consisting c fever and chills have been reported, including a case with nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxalo acetic transaminase following single doses of the drug. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procain amide therapy; and the patient should be instructe to report any soreness of the mouth, throat or gums unexplained fever or any symptoms of upper resp ratory tract infection. If any of these symptoms should occur and leukocyte counts indicate cellul depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately. Bitter taste, diarrhea, weal ness, mental depression, giddiness, psychosis wit hallucinations, and hypersensitivity reactions suc as angioneurotic edema and maculopapular rash have been reported.

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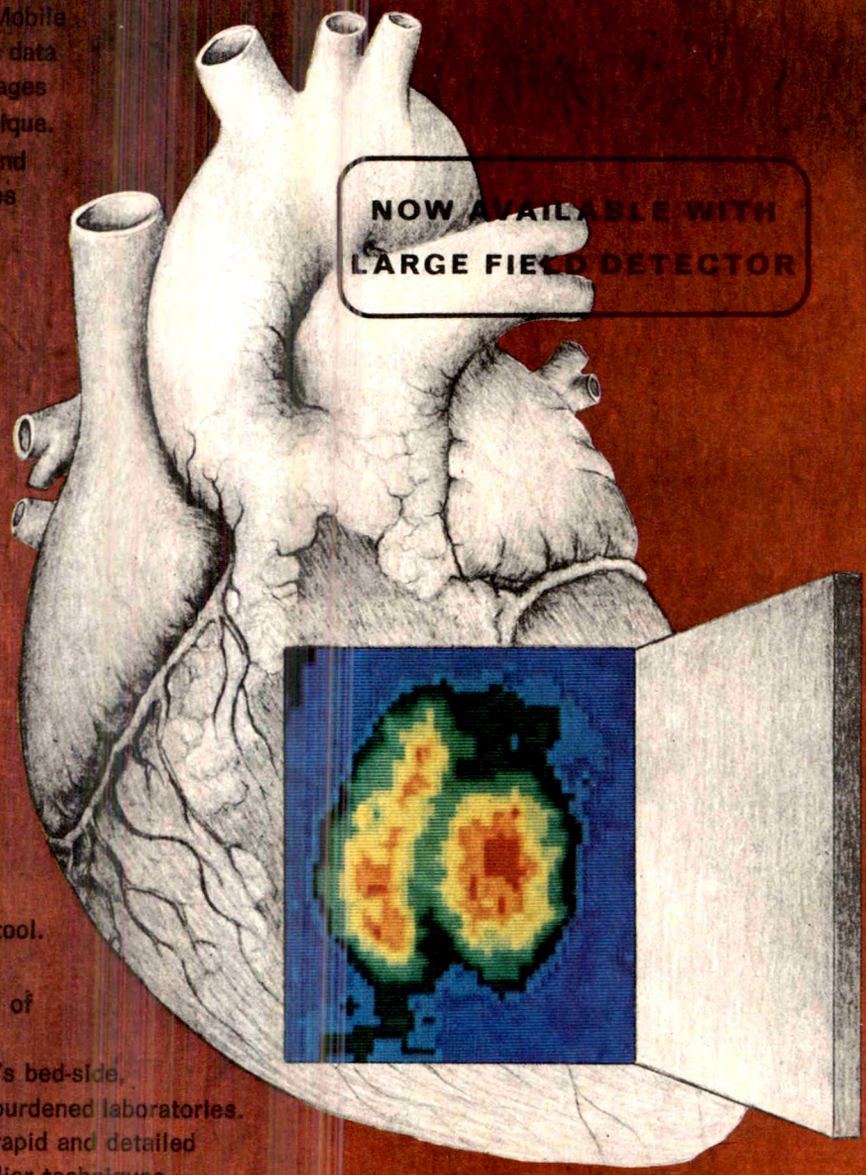

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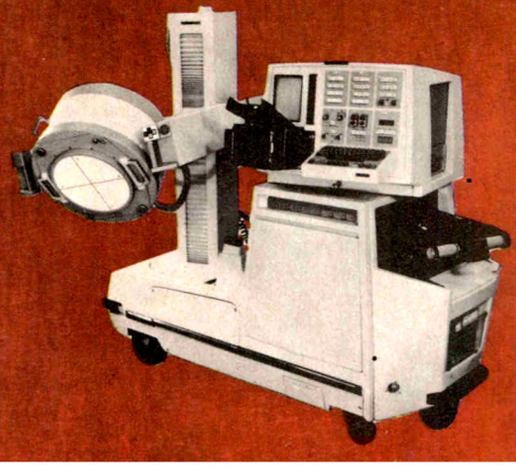

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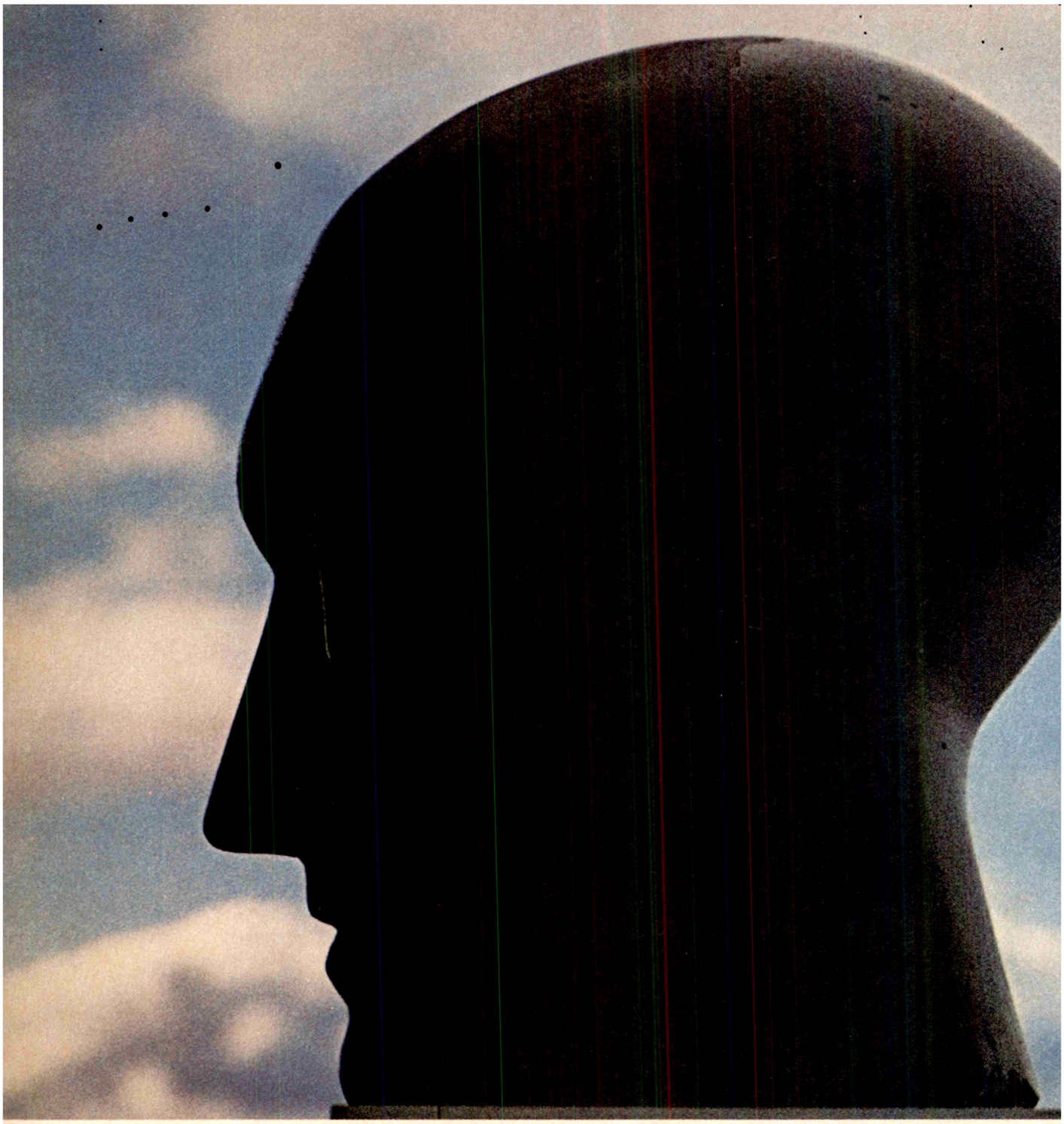

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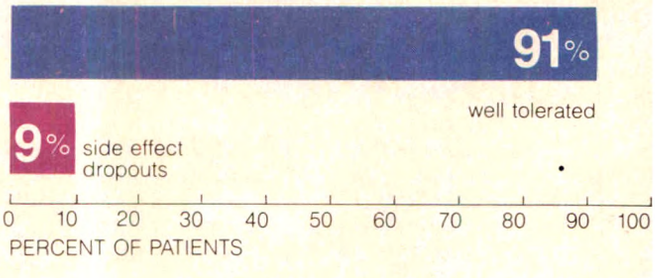

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Low incidence of depression, and orthostatic hypotension.*

The most common side effects are dry mouth, drowsiness, and sedation, which generally tend to diminish with time. As with other antihypertensives containing diuretic agents, hypokalemia, hyperuricemia, and hyperglycemia may occur. Drowsiness and sedation may be alleviated by giving the larger portion of the divided dose at bedtime.[2,3]

Convenient morning and bedtime dosage scheduling.

Combipres®

Each tablet contains: Catapres* (clonidine HCl) 0.1 or 0.2 mg. and chlorthalidone, 15 mg.

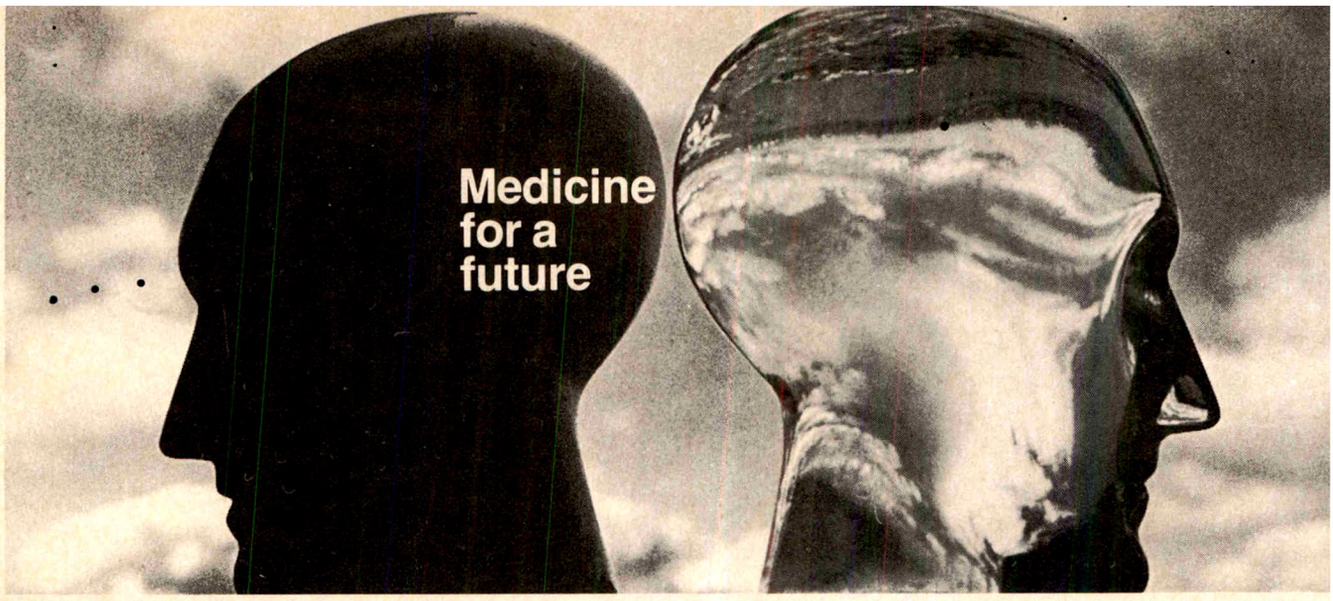
.1 and .2

HYPERTENSION

Combipres is not indicated for initial therapy. It is for patients responsive to its components given separately in equivalent dosages.

Please see brief summary of the prescribing information on the last page of this ad for warnings, precautions, and adverse reactions.

*Orthostatic hypotension has been reported with chlorthalidone and may be potentiated when chlorthalidone is combined with alcohol, barbiturates, or narcotics.



Combipres® .1 and .2

Each tablet contains: Catapres* (clonidine HCl) 0.1 or 0.2 mg, and chlorthalidone, 15 mg

Warning: This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

Indication: The drug is indicated in the treatment of hypertension (see box warning).

Contraindications: Patients with known hypersensitivity to chlorthalidone and patients with severe renal or hepatic diseases.

Warnings: Tolerance may develop in some instances necessitating a reevaluation of therapy.

Usage in Pregnancy: In view of embryotoxicity findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefit outweighs the potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of Combipres in children.

Precautions: When discontinuing Combipres, reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of Combipres therapy or by intravenous phentolamine.

Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect of the clonidine hydrochloride component.This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other antihypertensive agent, Combipres should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Combipres should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmological findings have been recorded with Catapres, in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Patients predisposed toward or affected by diabetes should be tested periodically while receiving Combipres, because of the hyperglycemic effect of chlorthalidone.

Because of the possibility of progression of renal failure, periodic determination of the BUN is indicated. If, in the physician's opinion, a rising BUN is significant, the drug should be stopped.

The chlorthalidone component of Combipres may lead to sodium and/or potassium depletion. Muscular weakness, muscle cramps, anorexia, nausea, vomiting, constipation, lethargy or mental confusion may occur. Severe dietary salt restriction is not recommended in patients receiving Combipres.

Periodic determinations of the serum potassium level will aid the physician in the detection of hypokalemia. Extra care should be given to detection of hypokalemia in patients receiving adrenal corticosteroids, ACTH or digitalis. Hypochloremic alkalosis often precedes other evidence of severe potassium deficiency. Frequently, therefore, more sensitive indicators than the potassium serum level are the serum bicarbonate and chloride concentrations. Also indicative of potassium depletion can be electrocardiographic alterations such as changes in conduction time, reduction in amplitude of the T wave; ST segment depression; prominent U wave. These abnormalities may appear with potassium depletion before the serum level of potassium decreases. To lessen the possibility of potassium deficiency, the diet, in addition to meat and vegetables, should include potassium-rich foods such as citrus fruits and bananas. If significant potassium depletion should occur during therapy, oral potassium supplements in the form of potassium chloride (3 to 4.5 gm/day), fruit juice and bananas should be given.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy.

Clonidine hydrochloride: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one case of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash; impotence, urinary retention; increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Chlorthalidone: Symptoms such as nausea, gastric irritation, anorexia, constipation and cramping, weakness, dizziness, transient myopia and restlessness are occasionally observed. Headache and impotence or dysuria may occur rarely. Orthostatic hypotension has been reported and may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics. Skin rashes, urticaria and purpura have been reported in a few instances.

A decreased glucose tolerance evidenced by hyperglycemia and glycosuria may develop inconsistently. This condition, usually reversible on discontinuation of therapy, responds to control with antidiabetic treatment. Diabetics and those predisposed should be checked regularly.

As with other diuretic agents hypokalemia may occur (see Precautions). Hyperuricemia may be observed on occasion and acute attacks of gout have been precipitated. In cases where prolonged and significant elevation of blood uric acid concentration is considered potentially deleterious, concomitant use of a uricosuric agent is effective in reversing hyperuricemia without loss of diuretic and/or antihypertensive activity.

Idiosyncratic drug reactions such as aplastic anemia, thrombocytopenia, leukopenia, agranulocytosis, and necrotizing angiitis have occurred, but are rare.

The remote possibility of pancreatitis should be considered when epigastric pain or unexplained gastrointestinal symptoms develop after prolonged administration.

Other adverse reactions which have been reported with this general class of compounds include: jaundice, xanthopsia, paresthesia and photosensitization.

Overdosage: *Catapres (clonidine hydrochloride).* Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals abolishes all effects of Catapres overdosage.

Chlorthalidone: Symptoms of overdosage include nausea, weakness, dizziness, and disturbances of electrolyte balance. There is no specific antidote, but gastric lavage is recommended, followed by supportive treatment. Where necessary, this may include intravenous dextrose and saline with potassium administered with caution.

How Supplied: Combipres* 0.1 (Each tablet contains clonidine hydrochloride 0.1 mg + chlorthalidone 15 mg). It is available as pink, oval, single-scored compressed tablets in bottles of 100.

Combipres* 0.2 (Each tablet contains clonidine hydrochloride 0.2 mg + chlorthalidone 15 mg). It is available as blue, oval, single-scored compressed tablets in bottles of 100.

For complete details, please see full prescribing information.

References:

1. Data on file at Boehringer Ingelheim Ltd.
2. Pettinger WA: NEJM, 293:1179, 1975.
3. Katz FH: Hosp Med, 13:34, 1977.

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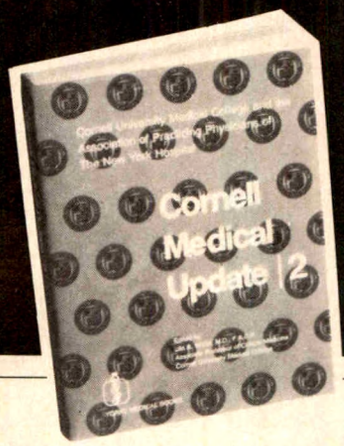

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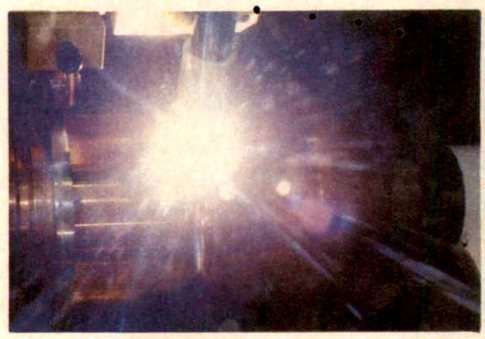

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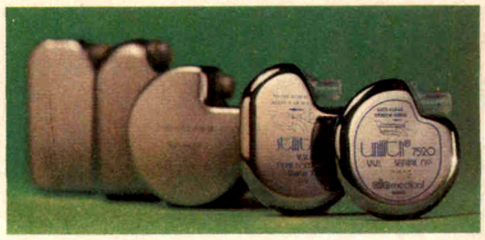

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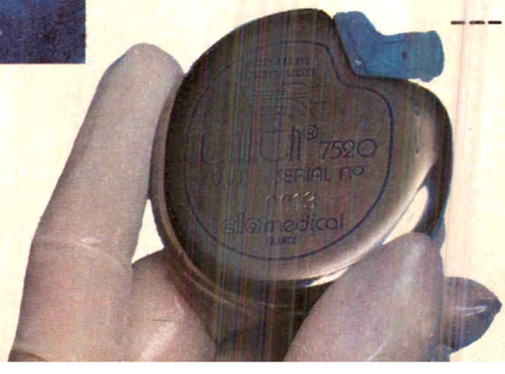

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Lasix® tablets, on the other hand, have a record of safety and efficacy that is exemplary—a record firmly established in almost 6,000 published papers. Since its introduction, 7.8 billion Lasix® tablets have been manufactured—without a product recall by the Government for any reason. Moreover, stability studies demonstrate that Lasix® tablets remain unimpaired in potency over a five-year period.†

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Lasix®—one less variable in the treatment of cardiac edema.

1. *HEW News,* publication 79-6. U.S. Department of Health, Education, and Welfare (Food and Drug Administration), March 30, 1979, p. 1.

†Data on file and available upon request from Hoechst-Roussel Pharmaceuticals Inc., Somerville, N.J. 08876.

Before prescribing, please consult complete product information, a summary of which appears on the following page.

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(furosemide)

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A brief summary of the Prescribing Information for Lasix (furosemide). Tablets 20, 40 and 80 mg.

WARNING: Lasix (furosemide) is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs.

INDICATIONS: Edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Hypertension when used alone or in combination with other antihypertensive drugs; patients not adequately controlled with thiazides also probably will not be adequately controlled with furosemide alone.

CONTRAINDICATIONS: Because animal reproductive studies have shown that furosemide may cause fetal abnormalities, the drug is contraindicated in women of childbearing potential. Anuria. History of hypersensitivity to the compound.

WARNINGS: Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Exercise care in patients receiving potassium-depleting steroids. Perform frequent serum electrolyte, CO_2, and BUN determinations during first few months of therapy and periodically thereafter, and correct abnormalities or temporarily withdraw the drug. Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital. Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Discontinue furosemide if increasing azotemia and oliguria occur during treatment of severe, progressive renal disease. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions. Furosemide may potentiate the therapeutic effect of other antihypertensive agents. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Exacerbation or activation of systemic lupus erythematosus may occur. Furosemide appears in breast milk. If use of the drug is essential, the patient should stop nursing. Cases of tinnitus and reversible hearing impairment have been reported.

There have also been some reports of cases in which irreversible hearing impairment occurred. Usually ototoxicity has been reported when furosemide was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were given. If the physician elects to use high-dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, an infusion rate not exceeding 4 mg furosemide per minute has been used.)

PRECAUTIONS: As with any effective diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Patients receiving furosemide should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with furosemide as with any other potent diuretic, especially with brisk diuresis, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis may exaggerate metabolic effects of hypokalemia, especially with reference to myocardial activity. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Periodic serum calcium levels should be obtained. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Furosemide has a tendency to antagonize the effects of tubocurarine and may potentiate the action of succinylcholine. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Furosemide may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

It has been reported in the literature that coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of Lasix (furosemide) in some patients. This effect has been attributed to inhibition of prostaglandin synthesis by indomethacin. Indomethacin may also affect plasma renin levels and aldosterone excretion; this should be borne in mind when a renin profile is evaluated in hypertensive patients. Patients receiving both indomethacin and Lasix (furosemide) should be observed closely to determine if the desired diuretic and/or antihypertensive effect of Lasix (furosemide) is achieved.

ADVERSE REACTIONS: Anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, blurred vision, tinnitus and hearing loss, anemia, leukopenia, agranulocytosis (rare), thrombocytopenia, aplastic anemia (rare), purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), exfoliative dermatitis, erythema multiforme, pruritus. Orthostatic hypotension may occur and may be exaggerated by alcohol, barbiturates, or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis.

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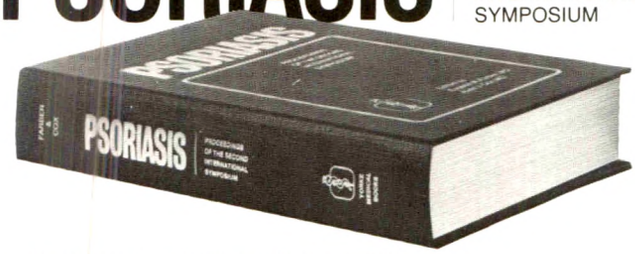

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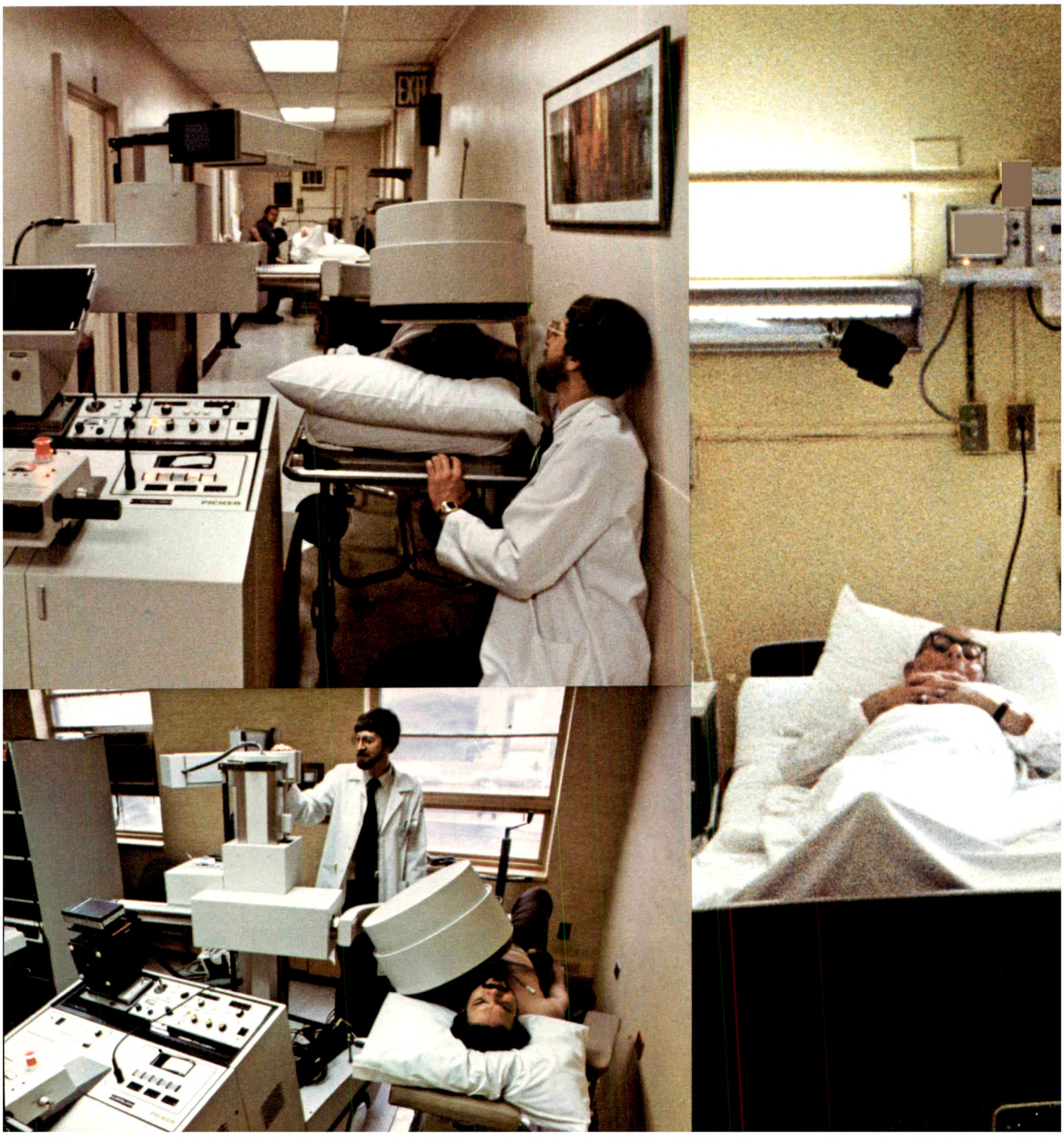

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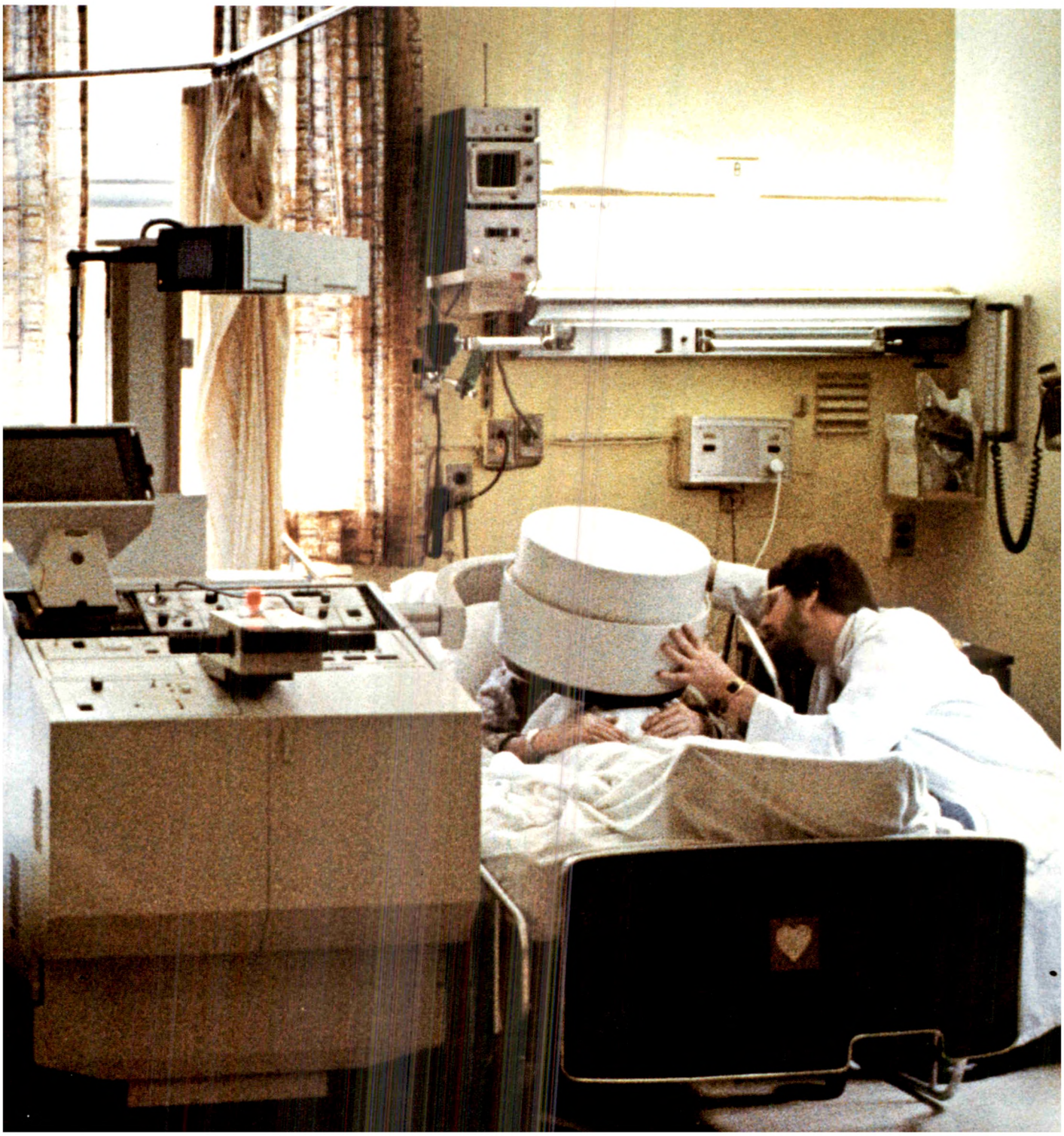

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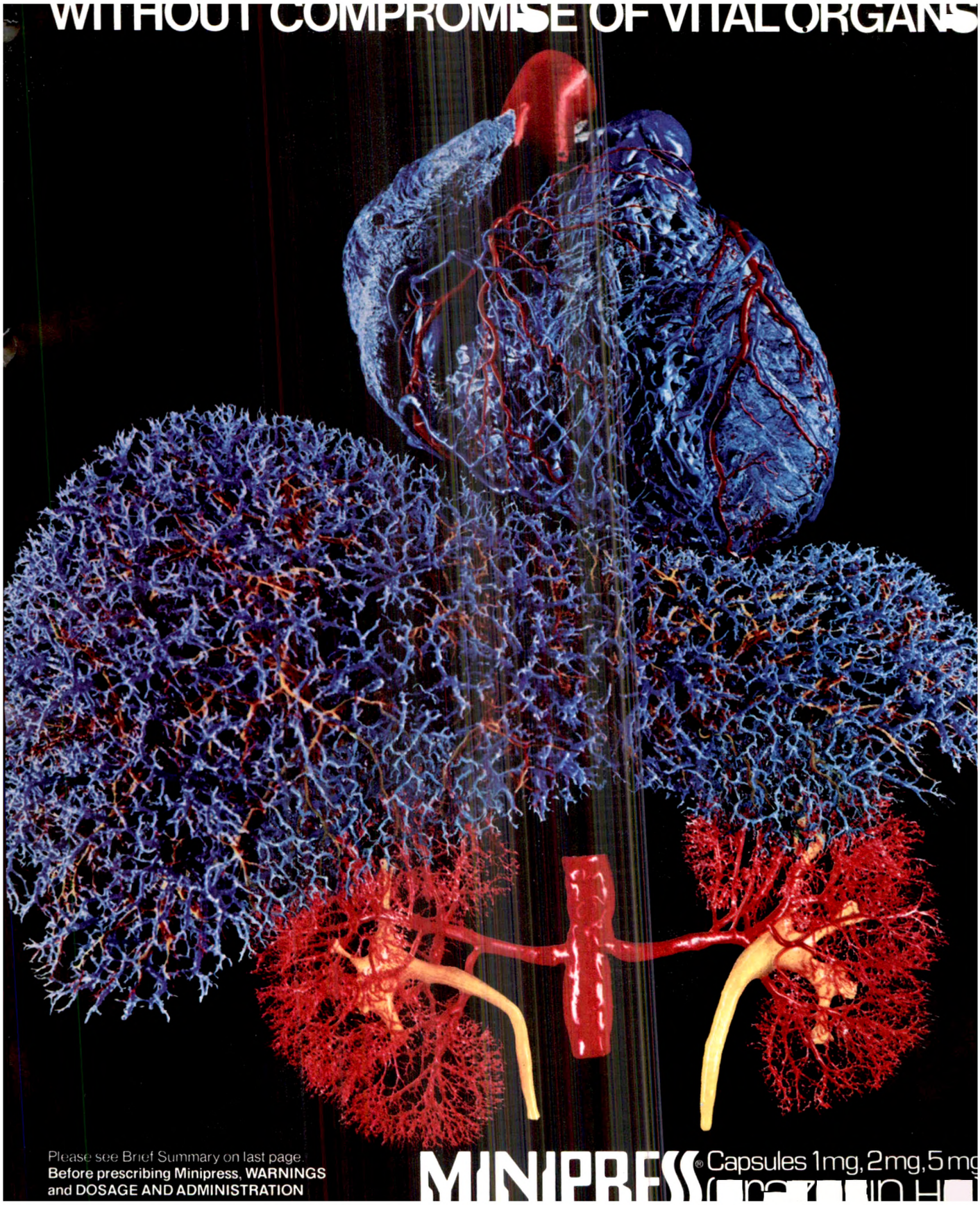
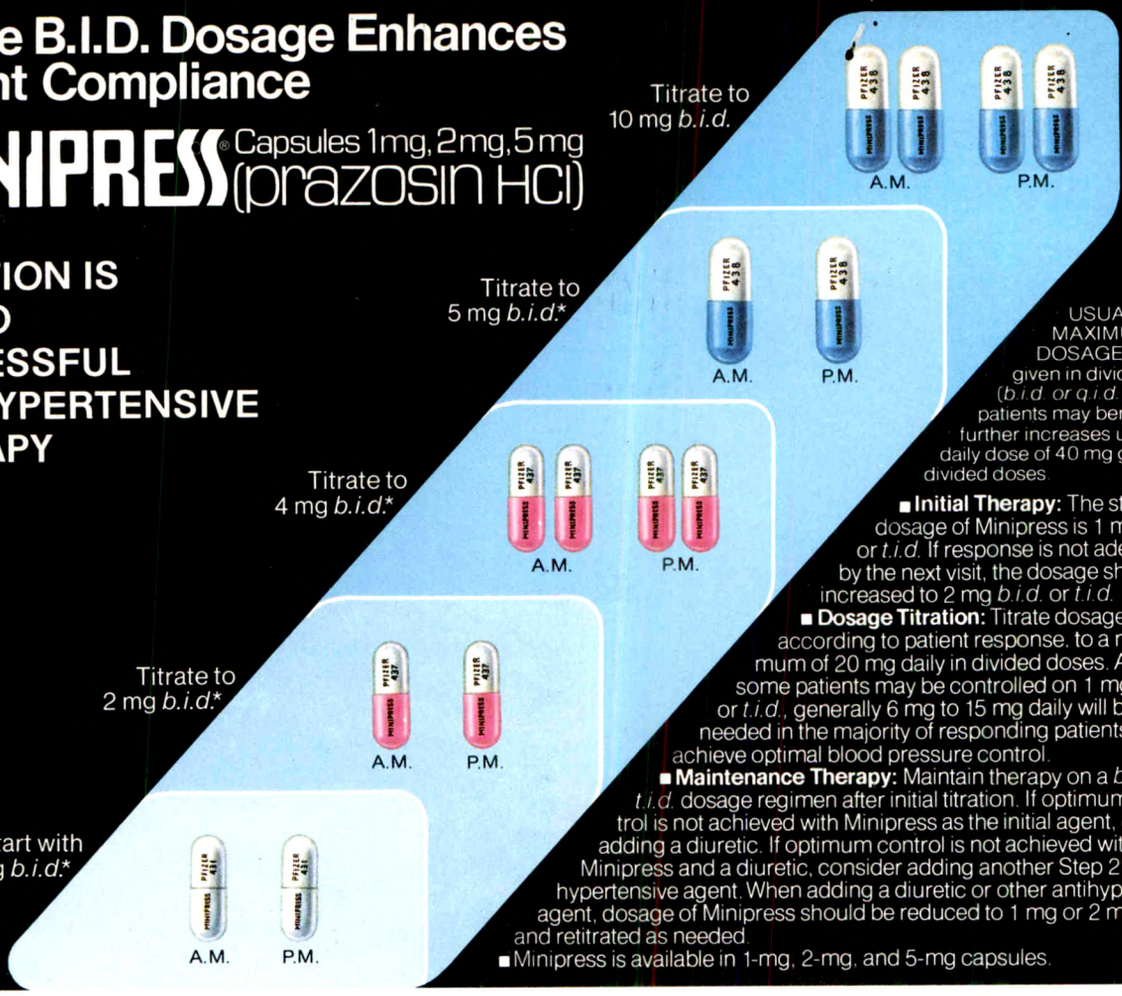

WITHOUT COMPROMISE OF VITAL ORGANS
Please see Brief Summary on last page.
Before prescribing Minipress, WARNINGS
and DOSAGE AND ADMINISTRATION
MINIPRESS® Capsules 1mg, 2mg, 5mg

Simple B.I.D. Dosage Enhances Patient Compliance

MINIPRESS® Capsules 1mg, 2mg, 5mg (prazosin HCl)

TITRATION IS KEY TO SUCCESSFUL ANTIHYPERTENSIVE THERAPY



*Or *t.i.d.*

USUAL MAXIMUM DAILY DOSAGE: 20 mg given in divided doses (*b.i.d.* or *q.i.d.*). A few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses.

■ **Initial Therapy:** The starting dosage of Minipress is 1 mg *b.i.d.* or *t.i.d.* If response is not adequate by the next visit, the dosage should be increased to 2 mg *b.i.d.* or *t.i.d.*

■ **Dosage Titration:** Titrate dosage slowly, according to patient response, to a maximum of 20 mg daily in divided doses. Although some patients may be controlled on 1 mg *b.i.d.* or *t.i.d.*, generally 6 mg to 15 mg daily will be needed in the majority of responding patients to achieve optimal blood pressure control.

■ **Maintenance Therapy:** Maintain therapy on a *b.i.d.* or *t.i.d.* dosage regimen after initial titration. If optimum control is not achieved with Minipress as the initial agent, consider adding a diuretic. If optimum control is not achieved with Minipress and a diuretic, consider adding another Step 2 antihypertensive agent. When adding a diuretic or other antihypertensive agent, dosage of Minipress should be reduced to 1 mg or 2 mg *t.i.d.* and retitrated as needed.

■ Minipress is available in 1-mg, 2-mg, and 5-mg capsules.

BRIEF SUMMARY

MINIPRESS® (prazosin hydrochloride) CAPSULES *For Oral Use*

INDICATIONS: MINIPRESS® (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

WARNINGS: MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS: The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established).

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, incontinence, impotence.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION: The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg two or three times a day. (See Warnings).

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED: MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).

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SPECIAL ARTICLE

Oxygen Deprivation and Early Myocardial Contractile Failure: A Reassessment of the Possible Role of Adenosine Triphosphate

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London, England

The precise mechanism responsible for early contractile failure after the onset of myocardial anoxia or ischemia has attracted speculation and controversy. The simple and attractive hypothesis that adenosine triphosphate (ATP) deficiency is responsible for this failure has often been dismissed on the basis of claims that there is only a small reduction in cell ATP content at a time when contractile activity is severely reduced. The premise of this article is that the changes in cell ATP content and distribution that theoretically should occur after oxygen depletion may not have been adequately considered and that previous measurements of cell ATP content may not have been carried out at the correct time.

Using an isolated rat heart preparation and high speed freeze-clamping techniques it has been possible to demonstrate that a substantial decrease in myocardial ATP and creatine phosphate content occurs after the onset of anoxia but *before* the onset of contractile failure. Thus, during the first 5 seconds of anoxia contractile activity remains constant whereas ATP decreases by 25 percent and creatine phosphate by 50 percent. Thereafter, contractile failure occurs and the rate of utilization of high energy phosphates declines with the cell content at a plateau or possibly increasing. These results are assessed in the light of the dynamic changes in energy metabolism occurring in early anoxia and suggest that ATP depletion in a specific cell compartment may be the primary trigger for early contractile failure.

Possible Mechanisms of Contractile Failure

The precise mechanism responsible for early contractile failure after the onset of myocardial ischemia or hypoxia (Fig. 1) has caused speculation and controversy for many years.[1–6] Although other mechanisms are not precluded three main and alternative theories have received serious consideration:

1. *Oxygen deprivation may induce changes in cardiac contractile proteins.*[2] However, because after even prolonged ischemia no irreversible damage has been detected in myofibrillar adenosine triphosphatase,[7] actomyosin,[8] myosin[9] or actin[10] and because the rapid contractile failure can be so readily and completely reversed, it seems unlikely that macromolecular changes could occur or account for the early contractile failure.

2. *A proton-induced change in calcium homeostasis has been suggested as a possible trigger for contractile failure.* Katz and Hecht[2] suggested that a decrease in intracellular pH may decrease the affinity of troponin for calcium and hence alter the calcium-mediated regulation of myofibrillar contraction and adenosine triphosphatase activity. However, it has been suggested[6,11] that more likely sites for interaction between calcium and protons are calcium entry during the action potential[12] and calcium release from the sarcoplasmic reticulum[13] or from superficial subsarcolemmal binding sites.[14] Convincing proof that a

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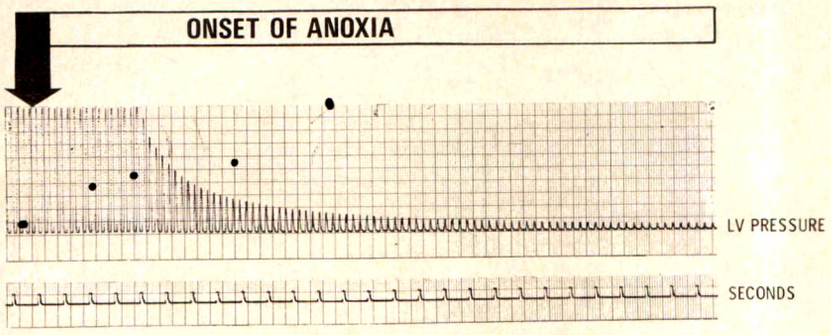

FIGURE 1. The abrupt contractile failure that occurs within seconds of the onset of anoxia. LV = left ventricular.

decrease in intracellular pH precedes, let alone triggers, contractile failure may be hampered by the difficulties of measuring intracellular pH meaningfully.[5,15] *However, other considerations may argue against intracellular pH as the primary trigger:*

a. There are apparently conflicting results indicating that both extracellular acidosis[16] and alkalosis[17] can exert protective effects during oxygen deprivation.

b. It has been claimed[4] that contractile failure occurs almost as rapidly in the anoxic myocardium (with maintained flow and washout of carbon dioxide and protons) as it does in the ischemic myocardium (with restricted washout).

c. It is possible that during the very early moments there may be a transient intracellular alkalosis resulting from proton-consuming[18,19] creatine phosphate breakdown.

d. Existing measurements and calculations of pH change during oxygen deprivation suggest a rather slow rate of decrease requiring a number of minutes as opposed to seconds.[5]

e. Perhaps the most convincing argument against the proposition that proton accumulation represents the primary lesion in contractile failure derives from a consideration of the potential sources of these protons.[19,20] Carbon dioxide-induced acidosis not only appears to develop slowly but also would not be expected to develop significantly during anoxia. Triglyceride and fatty acid metabolism may produce large numbers of protons[20] but it is unlikely to contribute during the early seconds of anoxia or ischemia. Net production of protons during anoxia- or ischemia-induced stimulation of glycolysis has been strongly challenged,[19] but in any event glycolytic stimulation would not appear to occur until 10 seconds or more after the onset of oxygen deprivation,[21] when significant contractile failure may have occurred. The most likely source of protons appears to be the net degradation of ATP. However, it has been strongly argued that[2,5,6] there is no decrease of ATP during the early moments of contractile failure and, even if such a decrease occurred, it would probably be supported by rephosphorylation from creatine phosphate, which is a proton-consuming[19] process. Finally, if net ATP degradation were responsible for proton generation, the acidosis would be secondary to the primary breakdown of ATP. This latter point serves to introduce the third mechanism as a candidate for early contractile failure.

3. *The depletion of ATP at some critical point of the excitation-contraction process could adequately explain the very rapid contractile failure.* Oxygen deprivation undoubtedly has an almost immediate effect on energy provision especially because the energy carriers have such a rapid rate of turnover in the normally beating cell. Thus, any interruption in their synthesis should lead to a rapid reduction in contraction or a rapid decline of cell levels. This simple and attractive hypothesis has been dismissed on the basis of reports[6,22,23] that show only a small reduction in cellular ATP content at a time when contractile activity is severely reduced. *Nevertheless the proponents of the ATP hypothesis have invoked several supportive arguments:*

a. There is strong evidence[4,24,25] that ATP exists in discrete cell compartments, some of which are distinct from creatine phosphate compartments. It has been proposed that depletion in one small compartment, not readily detected by conventional analytic methods, may be responsible for the interruption of contractile activity.

b. Kubler and Katz[4] have recently suggested that ATP, through its modulatory role in calcium movements, could reduce contractility without necessarily undergoing severe depletion.

c. Inorganic phosphate accumulation from high energy phosphate degradation has also been discussed by Kubler and Katz[4] as a possible explanation, suggesting that through amplification processes inorganic phosphate can translate a relatively small decline in high energy phosphate into a large signal for other metabolic processes.

It is the proposition of this paper and the preliminary data that it contains, that (1) the dismissal of ATP as a causative agent in early contractile failure may be based on experiments in which ATP content was measured at an inappropriate time, and (2) that the consideration of the expected changes in ATP content, in relation to rapidly changing patterns of ATP production and utilization, may have been somewhat incomplete.

Changing Patterns of ATP Utilization and Production: Determinants of Cell ATP Content (Fig. 2)

A review of the many studies on the aerobic isolated working rat heart[26] indicates a mean ventricular content of 20 to 25 μmoles ATP/g dry weight and 25 to 30

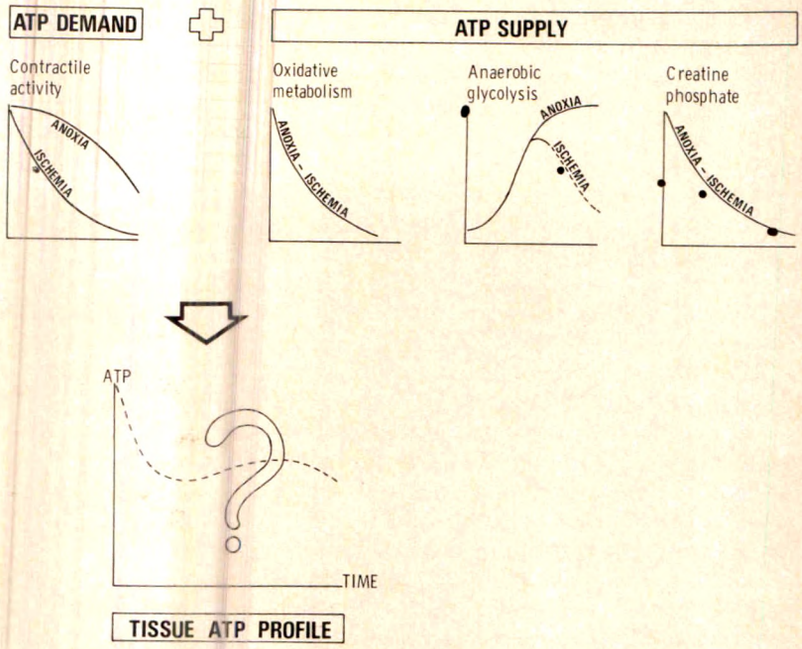

FIGURE 2. Major factors contributing to the cell content of adenosine triphosphate (ATP) after the onset of anoxia or ischemia. The graphs are not to scale, and their profiles are somewhat speculative.

μmoles creatine phosphate/g dry weight. On the basis of reported oxygen and substrate utilization values it is likely that approximately 300 to 400 μmoles of ATP is produced per minute per g dry weight. Thus, approximately 1 μmole of ATP/g dry weight may be consumed for each normal heartbeat. With exclusion of any unavailable compartments, the total heart content of ATP and creatine phosphate may therefore be sufficient to support 50 to 75 normal beats. If, therefore, all energy production were instantaneously halted then within 1 minute (even allowing for reduced utilization by beats of reduced amplitude) there should be nearly complete energy utilization and cardiac arrest. In a nonejecting rat heart preparation not performing external work, the energy requirements would be substantially lower; however, if energy production were instantly halted there should be rapid energy depletion and contractile failure.

Factors determining temporal ATP content of myocardial cell: After the onset of ischemia or anoxia, energy production is *not* suddenly halted. Dissolved oxygen in the cytoplasm and extracellular space together with that bound to residual hemoglobin will maintain oxidative metabolism and ATP production for several seconds at least. The decline of ATP will, in some compartments at least, be tempered by rephosphorylation from the creatine phosphate reserves. Superimposed on these factors determining the temporal ATP content of the cell will be the transient stimulation of glycolytic ATP production during ischemia or the continuing and substantial glycolytic ATP production associated with anoxia.[27] The combined effects of reduced contractile activity, enhanced glycolytic ATP production, creatine phosphate stores and residual oxidative ATP production will serve to decrease the rapid rate of decrease in ATP that would occur if production totally ceased and contractile activity were maintained.

The shape of the total ATP profile (Fig. 2) will thus depend on (1) the rate of decrease of oxidative ATP production; (2) the rate, extent and duration of glycolytic ATP production; (3) the proportion of ATP that is in equilibrium with creatine phosphate; and (4) the temporal relation between these three factors and the rate of decrease of ATP utilization due to the conservative effects of contractile failure. Indeed, at the outset of this study, and in view of the very rapid contractile failure observed at the onset of ischemia or anoxia, it seemed possible that there might even be an increase in ATP content at some point in some compartment. Such an increase might, of course, be masked by reductions in other compartments.

A search of published data failed to reveal any detailed studies of ATP determinations performed sooner than 10 or 15 seconds after the onset of oxygen deprivation. Failure to measure ATP earlier was presumably due to the observation of near normal levels at this time. However, it is during the early seconds that the critical contractile changes occur and, if the arguments presented in the preceding paragraphs are in any way correct, then major changes in the relative sizes and activities of various ATP compartments may occur during these early seconds and may have been missed by previous investigators. We therefore decided to investigate the metabolic changes occurring during the early seconds of anoxia-induced contractile failure.

Metabolic Changes During Early Seconds of Anoxia-Induced Contractile Failure

Methodologic Considerations

For these studies male rats (250 to 350 g body weight) of the Wistar strain were used for the preparation of an isolated perfused working heart. This model, which has been described in detail elsewhere,[26,28] is a left heart preparation in which oxygenated perfusion fluid enters

the cannulated left atrium at a pressure of 20 cm water and is passed to the ventricle, from which it is spontaneously ejected at a rate of 40 to 55 ml/min by way of an aortic cannula against a hydrostatic pressure of 100 cm water. When provided with adequate substrate and oxygen this preparation can be functionally and metabolically stable for considerable periods of time. Cardiac function can be assessed from measurements of aortic flow, coronary flow, heart rate, intraventricular pressure and its derivatives. Biochemical status can be assessed by freeze-clamping the tissue and taking it for extraction and metabolite analysis.

Immediately after mounting, the hearts were perfused aerobically (95 percent oxygen + 5 percent carbon dioxide) at 37° C with a Krebs Henseleit bicarbonate buffer[27,28] containing 11.1 mmoles glucose/liter. After a 7 minute period of aerobic perfusion, the hearts were subjected to anoxia by changing the perfusate from one gassed with 95 percent oxygen + 5 percent carbon dioxide to one gassed with 95 percent nitrogen + 5 percent carbon dioxide. This was accomplished with use of a two-way tap and a double reservoir system. The crossover taps were located adjacent to the cannulas and thus permitted an instantaneous (less than 0.5 second) change in the composition of the perfusate.

Measurements of contractile activity during the aerobic control period and the anoxic failure period were achieved with use of a pressure transducer attached to an open tip catheter introduced into the left ventricular cavity. In addition to providing measurements of peak systolic pressure, the first derivative of left ventricular pressure (dP/dt) and heart rate, this permitted the exact determination (by the interruption of the physiograph recording) of the time of sampling and the point in the cardiac cycle at which sampling occurred.

Tissue sampling of whole hearts during control or failure conditions was achieved using an electronically and pneumatically operated set of high speed (10 msec) freeze (−190° C) clamps based on those described by Wollenberger and co-workers.[29,30] Frozen tissue was taken for the determination[27,31] of ATP, creatine phosphate and tissue water and the results were expressed as μmoles/g dry weight.

Anoxia in the Working Rat Heart: Acute Metabolic and Functional Responses

Contractile activity: Contractile failure was monitored during the first 40 seconds of anoxia and Figure 3, top reveals that contractile activity remained essentially constant for the first 5 seconds of anoxia and then rapidly declined to less than 10 percent of the control value in the succeeding 10 seconds. After 20 seconds of anoxia there was a substantial recovery of contractile activity to approximately 45 percent of the control value. This value was then maintained for some time

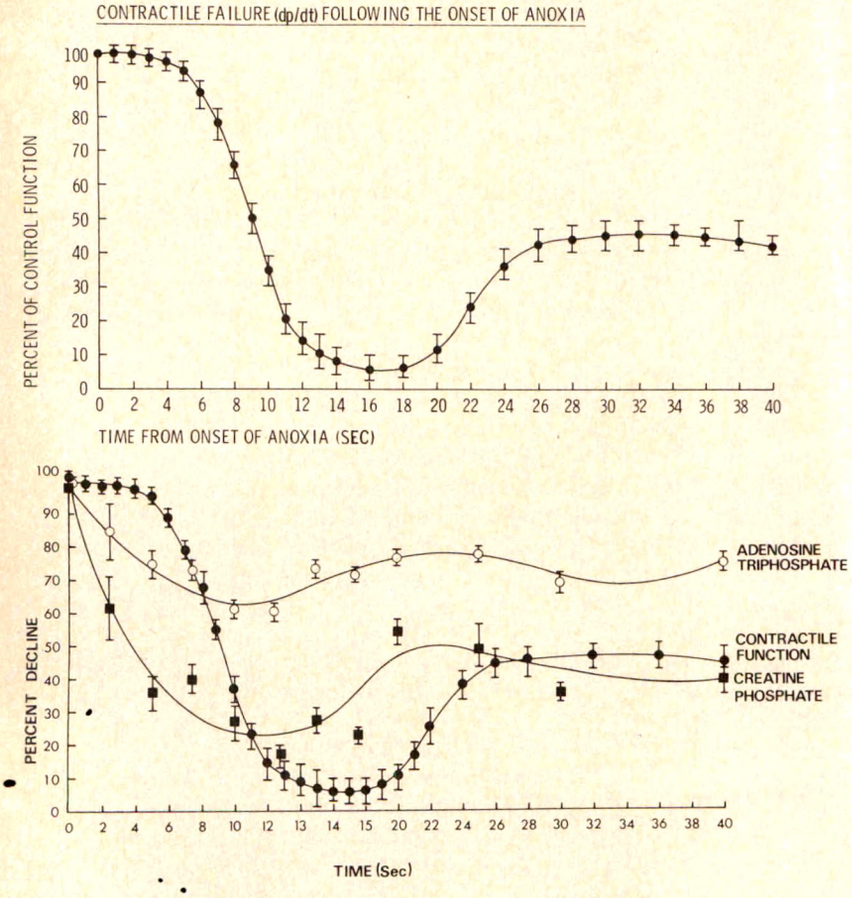

FIGURE 3. Top, the decline of contractile activity (first derivative of left ventricular pressure [dP/dt]) in the isolated perfused working rat heart after the onset (time 0 on the graph) of anoxia. Each **closed circle** represents the mean values of 12 hearts and the **bars** represent the standard deviations. **Bottom,** the relation between contractile failure (**closed circles**) and cytoplasmic adenosine triphosphate (ATP) (**open circles**) and creatine phosphate (**closed squares**) content during the first 40 seconds after the onset of anoxia. Each data point represents the mean values of at least six hearts, and the standard deviation is indicated by the **bars.**

before further progressive but slow failure occurred. The profile for contractile failure in Figure 3 illustrates dP/dt, but during the critical first 20 seconds of anoxia it is representative of other indexes of cardiac function such as peak systolic pressure and aortic flow rate.

Metabolic changes: Figure 3, bottom illustrates the changes that occur in the cell content of ATP and creatine phosphate during the first 40 seconds of anoxia (at least six hearts were sampled at each time point). It is apparent that the declines are not simple but multiphasic with a sharp reduction in both ATP and creatine phosphate between 0 and 10 seconds and a subsequent increase between 15 and 30 seconds, followed by a relatively stable value between 30 and 40 seconds that, in the case of ATP is only about 20 percent less than control value.

These results illustrate a number of important points: (1) There is a marked decrease in high energy phosphate content that *precedes* any reduction in contractile activity. Thus by 5 seconds ATP has decreased by approximately 25 percent and creatine phosphate by approximately 50 percent. (2) The rapid decline of contractile activity that occurs between 5 and 10 seconds is accompanied by a continuing but reduced rate of reduction of ATP and creatine phosphate. (3) In the period from 10 to 15 seconds, contractile failure is almost complete and ATP and creatine phosphate no longer decrease but establish transient plateau levels. (4) In the period from 15 to 20 seconds there is a secondary increase in ATP and creatine phosphate content with a rise of 15 and 30 percent, respectively. During this period there is little or no contractile activity. (5) The increase in ATP and creatine phosphate is followed in the period from 20 to 25 seconds by an increase in contractile activity. (6) In the period from 25 to 40 seconds (and later), a relatively stable equilibrium appears to be attained with contractile activity at 40 to 50 percent of the control value, ATP at 70 to 80 percent of the control value and creatine phosphate at 35 to 45 percent of the control value. Although not shown in Figure 3 this is followed by a slow but progressive decrease in all variables.

Comments and Possible Interpretations

The multiphasic nature of the adenosine triphosphate (ATP) and creatine phosphate profile may explain why the important and early reduction of these phosphates may have been missed in earlier studies. For example, the ATP and creatine phosphate content of the myocardium is essentially identical 40, 20 and 5 seconds after the onset of anoxia. However, between these three values are major elevations and depressions of the content. Thus the detection of only a 20 to 25 percent decrease in ATP content after 20 to 40 seconds of anoxia may have prevented investigators from making earlier measurements.

The sharp decrease of ATP and creatine phosphate during the first 5 seconds of anoxia undoubtedly reflects the anoxia-induced shutdown of oxidative ATP production in the presence of continued ATP utilization (contractile activity during this 5 second period is maintained at control levels). In fact, the decrease in ATP and creatine phosphate (CP) would probably be more rapid if it were not for the residual (dissolved oxygen) oxidative metabolism that must inevitably be maintained for a few seconds. Nonetheless, during this 5 second period (about 25 beats) it can be calculated that approximately 20 to 25 μmoles of ATP plus CP is consumed per gram dry weight of heart, a figure that would agree well with the value of 1 μmole/beat per g dry weight proposed earlier, in the introduction to this article.

Compartment versus conservation theory of energy depletion: After 5 seconds or when the ATP has decreased by 25 percent and creatine phosphate by 50 percent there is an abrupt decline of contractile activity, and associated with this decline during the period from 5 to 10 seconds, is a reduction in the rate of utilization of both phosphates. At this stage it is not possible to state categorically whether the decline in the rate of decrease of these phosphates is due to the near depletion of the high energy phosphate in a relatively small compartment (perhaps 25 to 40 percent of the cell's normal ATP content) that specifically supports contractile activity. Alternatively, the decline of ATP and creatine phosphate utilization may reflect a reduced energy requirement as a consequence of the now rapidly declining contractile activity. Thus, contractile activity may decrease because of energy depletion in a critical compartment ("the compartment theory") or energy depletion may be decreased as a result of a specific reduction of contractile activity ("the conservation theory"). In all liklihood both of these factors contribute to the energy and the contractile profiles because compartmentalization of ATP and creatine phosphate undoubtedly exists[25] and because the reduction of contractility must reduce energy utilization.

Secondary increase in high energy phosphates at 10 to 20 seconds: The observation that after the early phase of contractile failure and energy depletion, there is a secondary increase in ATP (by approximately 15 percent) and creatine phosphate content (by approximately 30 percent) during the period from 10 to 20 seconds can probably be adequately explained and, as indicated in our introduction, should possibly be expected. Anoxic perfusion with a glucose-containing medium rapidly and markedly stimulates glycolysis and anaerobic ATP production. Studies by Williamson[21] in the anoxic rat heart indicate that this stimulation becomes operative after about 10 seconds of anoxia. Thus, during the period from 10 to 20 seconds, when there is little or no energy-consuming contractile activity (and possibly still a little residual oxidative ATP production) and substantial glycolytic ATP production, the cell content of high energy phosphates is able to increase.

Repletion of ATP and secondary recovery of contractile activity: After 20 seconds or so, ATP and creatine phosphate have returned to approximately 75 and 50 percent, respectively, of their control values. *At this point* there is a resumption of contractile activity that rapidly returns to 40 to 50 percent of the control value and, after 30 seconds, ATP, creatine phosphate

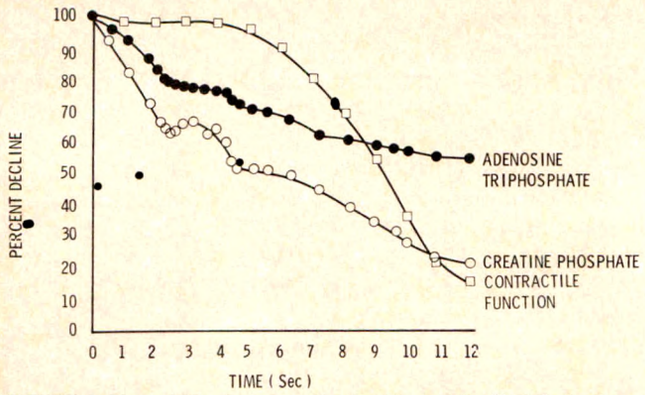

FIGURE 4. The relation between contractile activity (first derivatives of left ventricular pressure [dP/dt]) (**open squares**), ATP (**closed circles**) and creatine phosphate (**open circles**) during the first 12 seconds of anoxia. Each curve is based on samples of 70 hearts and the resultant profile for ATP and creatine phosphate is derived from a computer analysis of the best fit line derived from a modification of the standard least squares method.

and contractile activity establish a relatively stable new equilibrium that gradually deteriorates over the succeeding minutes. It is of particular interest that the contractile activity resumes when the ATP and creatine phosphate contents return almost to the identical values recorded at the time of initial contractile failure. This may well indicate the existence of a compartment representing 25 to 35 percent of the cells' most vulnerable ATP (in equilibrium with 60 to 80 percent of the cells' creatine phosphate), which may be responsible for the control of contractile activity. The depletion of this compartment may result in contractile failure and the repletion in contractile recovery. In addition to indicating the existence of a critical compartment of ATP, the secondary recovery of contractile activity again indicates that major changes in high energy phosphates precede any contractile changes.

Further Confirmation of the Critical Changes

The critical claim in the preceding section that during the first 10 seconds of anoxia ATP and creatine phosphate changes precede any contractile changes were based on relatively few hearts analyzed after 2.5, 5, 7.5 and 10 seconds of anoxia. To confirm this important aspect of these studies it was decided to freeze-clamp and assay a large number of hearts (no. = 70) during the first 12 seconds of anoxia. In view of the difficulty of undertaking repetitive and very rapid freeze-clamping at specific times a random clamping method was adopted. The precise time of clamping was then determined retrospectively from the point of interruption of a physiograph recording. Figure 4 shows the results obtained when the 70 values for ATP and creatine phosphate were entered into a computer program that calculated and plotted the best fit line by a modification of the standard least squares method (corrected for an uneven distribution of sampling). The results confirmed the earlier report that ATP decreased by 25 percent and creatine phosphate by 50 percent during the first 5 seconds of anoxia and that during the subsequent 5 seconds (when contractile activity decreased from 95 to 35 percent) ATP decreased further to 55 percent of control value and creatine phosphate to 25 percent of control value. It is clear that a major reduction of energy reserves precedes and accompanies the anoxia-induced decline of contractile activity.

Although not understood at this stage, the sample numbers and closeness of fit suggested that the various inflections in the profiles of ATP and creatine phosphate decline were significant.

Concluding Comments

These results show that in the anoxic working rat heart, the decline of contractile activity is *preceded* by a major decline in the mean cell content of ATP and creatine phosphate. The true magnitude of the metabolic change is likely to be masked by compartmentalization and by anoxic ATP production. Although it is tempting at this stage to claim that ATP is the *primary* agent controlling contractile failure, additional studies with other models under different conditions will be required before final confirmation can be considered. Proponents of the proton hypothesis may still claim, possibly correctly, that net ATP degradation produces protons that are ultimately responsible for the contractile failure. This may well be the case, but until it is resolved whether the rapid, complex and interrelated exchange and breakdown of ATP and creatine phosphate during the first 10 seconds of anoxia is proton-generating or proton-consuming, the simple and attractive hypothesis that energy limits contractility should perhaps be adopted.

Acknowledgment

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Straddling and Overriding Atrioventricular Valves: Morphology and Classification

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Fifty-seven hearts are described in which either the orifice or tension apparatus of an atrioventricular (A-V) valve was related to both sides of a septum in the ventricular mass. In most of the hearts both the orifice overrode the septum and the tension apparatus straddled the septum. In some hearts straddling of the tension apparatus was present in the absence of overriding of the anulus while in two hearts the anulus overrode in the absence of straddling. Hearts were observed in which the chamber receiving all of one valve and the straddling portion of the other valve had either right or left ventricular morphologic features, and in each type the chamber receiving only part of the straddling valve was found either to the right or the left. When the straddling valve was morphologically a tricuspid valve it always straddled the posterior part of a septum that never extended to the crux; when it was morphologically a mitral valve it always straddled the anterior part of a septum that did extend to the crux. This arrangement was found irrespective of the relations of the chambers.

Four basic groups were therefore defined: straddling of the mitral and tricuspid valves in the setting of A-V concordance and discordance, respectively. However, the degree of override of the straddling valve was frequently such that the A-V connection present was double inlet ventricle rather than concordance or discordance. Indeed, in each group a series of anomalous hearts was found between the extremes of concordance or discordance and double inlet. In categorizing the A-V connections, these series were divided at their mid points. The hearts with double inlet connections were considered univentricular hearts and their chambers described accordingly. In each series hearts were found with unequally committed common valves that were virtually identical to the hearts with straddling right or left valves. They were therefore included in the study as were two hearts in which both right and left valves straddled. Examination of the conduction tissues in examples of each series showed that the position of the connecting node depended on whether or not the septum extended to the crux, anterior systems being found when it did not and either anterior or regular systems when it did, the latter variation depending on the A-V connection present. The study shows that straddling or overriding valves can be easily catalogued if attention is paid to the A-V connection and the morphologic features and relations of the ventricular chambers.

A straddling atrioventricular (A-V) valve is a valve whose tension apparatus takes origin from both sides of the ventricular septum so that its orifice is usually above two chambers in the ventricular mass. Within such a definition a common A-V valve nearly always straddles, but for semantic reasons there is no agreement whether such a valve should be considered a straddling valve. Liberthson et al.[1] reserved the term "straddling" for the description of either the mitral or tricuspid valve when its papillary muscles were attached to both sides of a septum.

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Straddling of one of these valves is of major surgical significance, and for this reason its preoperative diagnosis is desirable.

Such straddling was probably first described by Lambert,[2,3] but cases of straddling valves have subsequently been described by several investigators.[1,4–8] Interest in the malformation has become focused recently by its more frequent identification during echocardiographic investigation.[9–12] Despite this interest, there is still considerable disagreement concerning the morphologic features of these valves and their classification, particularly with regard to their relation to the univentricular heart.[1,4,6,7,13] For this reason we have studied the morphology of hearts with straddling valves from various centers in the United Kingdom and Holland, and determined the disposition of their conduction tissues. Our findings and a suggested classification for straddling valve form the subject of this report.

Selection Criteria and Descriptive Terms

Valve overriding versus straddling: It became clear during the early part of our study that it was necessary to distinguish between a valve whose orifice was committed to two chambers in the ventricular mass and a valve whose tension apparatus arose from both sides of a septum in the ventricular mass. We have termed the first of these situations *overriding* of the valve anulus (Fig. 1a) and the second *straddling* of the valve tension apparatus (Fig. 1b). A valve can have both straddling of its tension apparatus and override of its anulus (Fig. 1b). Equally a valve anulus can override without straddling of its tension apparatus when all its papillary muscles arise from only one ventricular chamber despite the orifice being committed to both chambers (Fig. 1c). Similarly the tension apparatus can straddle in the absence of anular overriding when the orifice drains to only one chamber but the papillary muscles are attached to both sides of the septum (Fig. 1d).

The hearts chosen for study were therefore all those hearts within our collections that satisfied the criteria for straddling and overriding, straddling alone or overriding alone. As will be seen, most hearts studied exhibited the combination of both straddling and overriding, fewer hearts being examined with straddling alone and only two hearts with overriding alone. During this investigation we encountered several hearts in which one valve straddled, connecting one atrium with two chambers in the ventricular mass, while the other atrium ended blind (absence of one A-V connection or valve atresia). Such hearts have previously been described[1,14,15] but present special problems in description and categorization. For this reason we have excluded these hearts from the present study, preferring to report on them separately in a work in preparation.

Descriptive terms for ventricular chambers: With exclusion of the cases with an absent connection, the occurrence of a straddling or overriding valve or both, produces the situation whereby one chamber in the ventricular mass receives all of one A-V valve and part of the straddling or overriding valve (or else the greater part of an unequally committed common valve). The other chamber then has the remaining part of the straddling or overriding valve (or else the smaller part of the unequally committed common valve). So as to simplify descriptions of these chambers, because the chamber receiving only part of the straddling or overriding valve can vary markedly in morphologic features, we have used overall descriptive terms for the chambers. Thus the chamber receiving all of one valve and part of the other (or the larger part of a common valve) is termed the primary chamber whereas the chamber receiving only part of a valve (or the smaller part of a common valve) is termed the secondary chamber. The usage of these terms does not indicate that they are alternative terms for ventricles or rudimentary chambers. Primary chambers are always ventricles. According to our observations

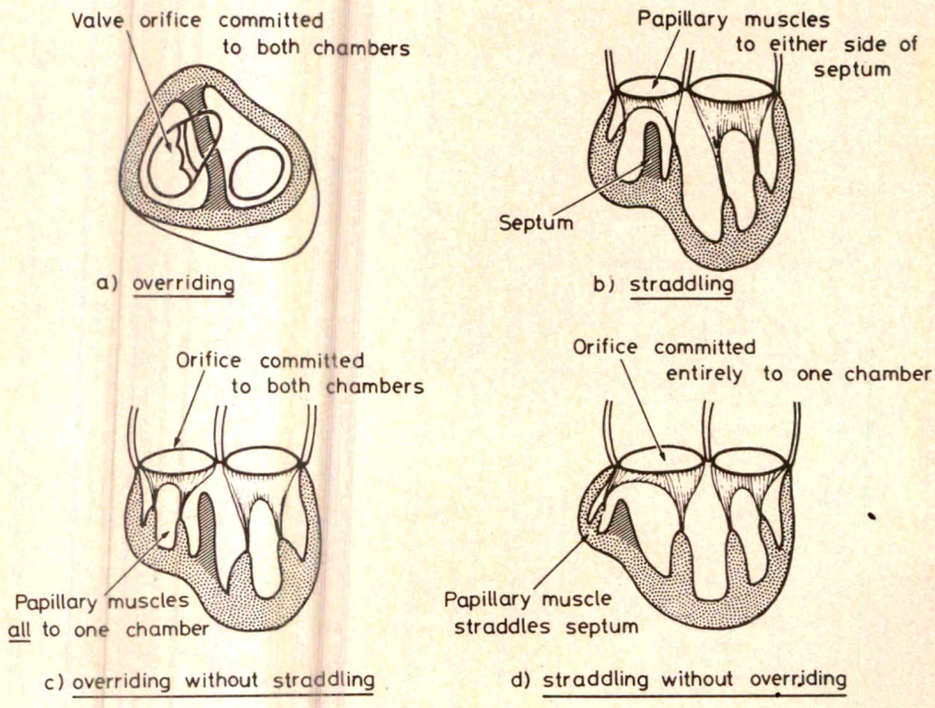

FIGURE 1. Diagram illustrating the terms overriding and straddling as used in this presentation. Overriding (**a**) describes the relation of the valve anulus to a septum, whereas straddling (**b**) describes the situation when the valve tension apparatus is attached to both sides of a septum. Usually a valve will both override and straddle (**b**). However, it is possible for overriding to exist in the absence of straddling (**c**) or straddling to be present without overriding (**d**). The **hatched** area represents the septum.

secondary chambers can be either ventricles or rudimentary chambers. Instead, the terms primary and secondary are used as literary devices to simplify description and grouping of the hearts examined. When both valves straddle, as occurred in two hearts, then clearly these devices are no longer applicable.

A-V connections: As we have described elsewhere[16] it is our contention that the degree of override of a valve determines the connection. This is the case with arterial valves, as indicated by Kirklin et al.[17] Our study has suggested to us that this is also the case with A-V valves. Thus, when more than half of a straddling A-V valve overrode the primary chamber then the connection was considered to be double inlet. Because there is agreement that one criterion of a single ventricle[18] is the presence of double inlet, we also considered the secondary chamber in such hearts to be rudimentary and the heart itself to be univentricular. When the straddling valve overrode the primary chamber by less than 50 percent then both chambers were considered to be ventricles and the A-V connection was categorized as concordant, discordant or ambiguous depending on the nature of the atria and ventricular chambers.[16]

Morphology of primary and secondary chambers: Our observations also showed that the morphologic features of either the primary or secondary chamber could vary according to the nature of its trabecular zones. Either chamber could be of a right or left ventricular type, the two types always being complementary, that is, a right ventricular secondary chamber with a left ventricular primary chamber or vice-versa. The trabecular pattern of the chambers was the criterion used in determining the ventriculoarterial connection present.

Common valve versus straddling valve: We also noted during our study that several hearts with common valves were markedly similar to hearts with straddling valves. But Liberthson et al.[1] excluded common valves from the category of straddling valves for semantic reasons. While noting this point, we also considered it important to remember that a common valve does not always straddle a septum. For example, in univentricular hearts with a rudimentary second chamber a common valve can be committed entirely to the main ventricular chamber (Fig. 2b). Equally, the common valve may be committed mostly to the main chamber and minimally to the rudimentary chamber (Fig. 2d). We considered that the latter arrangement was directly comparable to the anatomy seen with straddling of either the right or left A-V valves, as indeed was implied by Liberthson et al.[1] Because of this we have chosen to include these hearts within our study group. In contrast, we have not included hearts with a common valve where either the mitral or tricuspid component is recognizable as such but hypoplastic and committed in its entirety (Fig. 2c) to a hypoplastic right or left ventricle.[19]

Orientation of septum: In examining the hearts with straddling or overriding valves we took particular cognizance of the orientation of the septum straddled. We were concerned

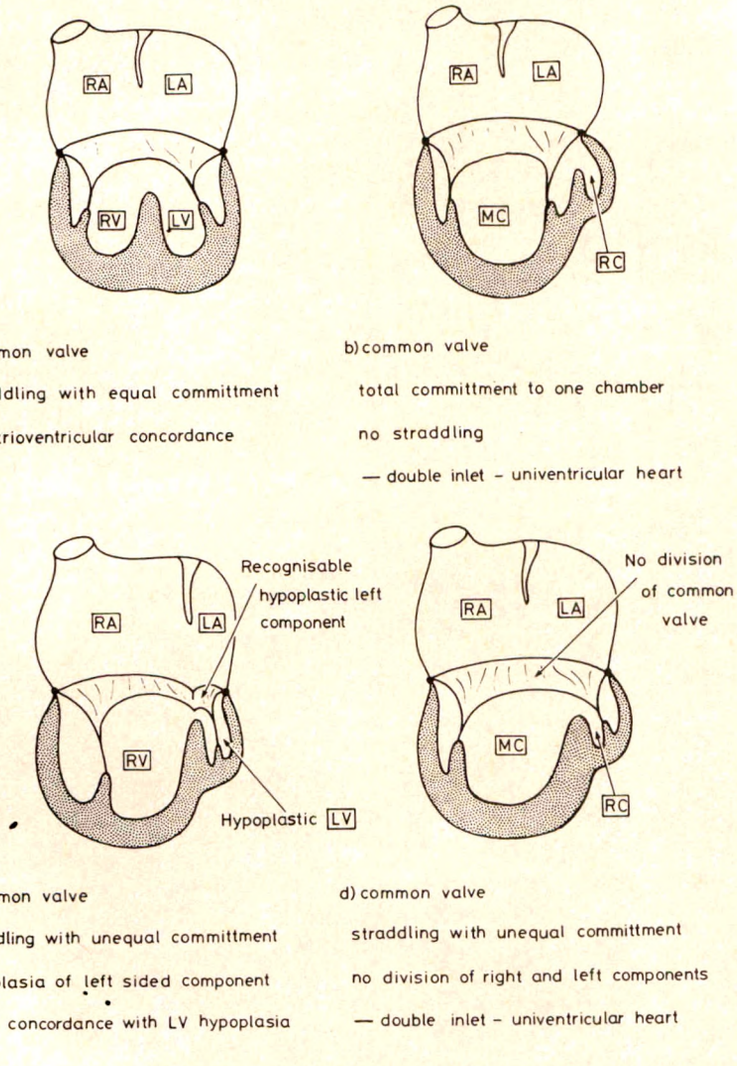

FIGURE 2. Diagram illustrating the problems that occur with a common valve in relation to its straddling. Nearly always a common valve has tension apparatus attached to both sides of a septum (**a**) (straddling as defined herein). But a common valve does not always straddle (for example, in a univentricular heart [**b**]). Frequently a common valve may have either its tricuspid or mitral component grossly reduced in size in association with hypoplasia of either the right or the left side of the heart[19] (**c**). None of the anomalies represented in panels **a** to **c** have been included in this study. However, other hearts were encountered in which a common valve was unequally committed between two chambers, the chambers being directly comparable with the primary and secondary chambers observed in the heart examined with straddling right or left valves. These hearts (**d**) were included in our study. AV = atrioventricular; LA = left atrium; LV = left ventricle; MC = primary chamber; RA = right atrium; RC = rudimentary chamber; RV = right ventricle.

as to whether the septum extended to the crux cordis (the point where the atrial septum or interatrial groove abuts on the A-V sulcus) or to another point on the A-V junctions. For naming other points, we related them to the acute point of the junction (site of descent in the normal heart of the acute marginal artery) or to the obtuse area of the junction.

Case Material

In all, 57 hearts that fulfilled the criteria for straddling or overriding as defined were examined. They came from the cardiopathologic collections of the Brompton Hospital, London; Hospital for Sick Children, London; Royal Liverpool Children's Hospital; Killingbeck Hospital, Leeds; Grimsby General Hospital; Wilhelmina Gasthuis, Amsterdam; State University of Leiden; and the Sint Antonius Ziekenhuis, Utrecht. Selected hearts from each group (see later) were studied so as to determine the disposition of their conduction tissues according to the technique outlined by Smith et al.[20]

Results

Straddling Valves

The hearts studied could be separated into four basic groups (Fig. 3). The groups were hearts with the left ventricular chamber to the left and straddling of either the right or the left valve and hearts with the left ventricular chamber to the right and straddling of either the right or the left valve. Each of the four groups could exist with either a double inlet atrioventricular (A-V) connection or a concordant or discordant connection, the latter depending on the nature of the chambers. An alternate way of grouping the hearts is to consider them in terms of those with primary chambers of right ventricular type (Fig. 3, a and d) and those with primary chambers of left ventricular type (Fig. 3, b and c). Because of some minor variation in position of the secondary chamber the hearts will be described in order based on primary chamber morphology.

Primary chamber of right ventricular morphology: *Straddling left valve and left-sided secondary chamber:* All hearts examined were from patients with situs solitus. The precise segmental arrangement and associated anomalies of the 12 hearts examined are shown in Table I. In each heart the straddling valve had the morphologic features of a mitral valve. The valve was committed predominantly to the secondary chamber in 11 cases, making the A-V connection concordant within our definitions (Fig. 4, a and b). In the other heart the straddling valve opened predominantly into the primary chamber along with the right A-V valve, making the A-V connection double inlet and the secondary chamber rudimentary (Fig. 5, a and b).

Irrespective of the degree of straddling, the septum between chambers always extended to the crux cordis. This was a consequence of the particular anatomy of the hearts because the valve straddled the anterior part of the septum in each case, the posterior part of the septum being uninvolved in the straddling process. The anterior and posterior margins of the septum were marked externally by the anterior descending branch of the left coronary artery and the posterior descending coronary artery, respectively. The size of the trabecular component of the secondary chamber varied depending on the degree of overriding, being larger in the biventricular hearts. However, in all instances an unequivocally left trabecular zone could be identified in the secondary chamber (Fig. 4b and 5b). On gross inspection the left ventricular conduction tissue could be identified ascending toward the crux. In one univentricular heart examined histologically the connecting A-V node was

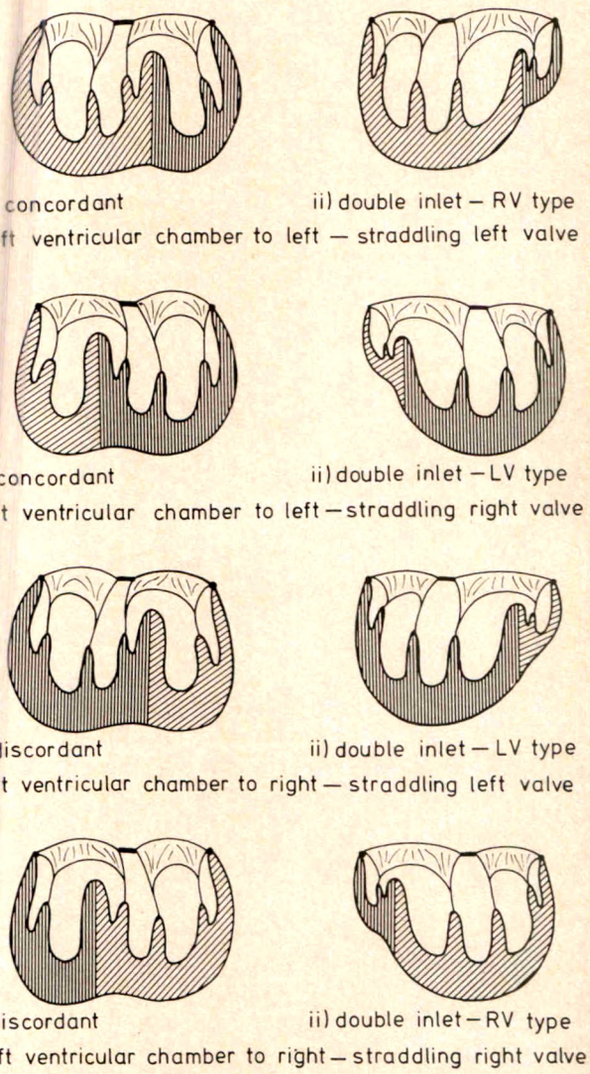

FIGURE 3. Diagrams illustrating the chamber combinations observed in the hearts studied with straddling right or left atrioventricular (A-V) valves. It should be anticipated that the same combinations may be found with straddling of a common valve. Four basic patterns exist: straddling mitral valve in the setting of A-V concordance (**ai**), this being part of a series extending to straddling left valve in double inlet univentricular heart of right ventricular (RV) type (**aii**) with a left-sided rudimentary chamber; straddling tricuspid valve in the setting of A-V concordance (**bi**) extending into straddling right valve with double inlet univentricular heart of left ventricular (LV) type with a right-sided rudimentary chamber (**bii**); straddling tricuspid valve in A-V discordance (**ci**) extending into straddling left valve in double inlet univentricular heart of left ventricular type with a right-sided rudimentary chamber (**cii**); and finally straddling mitral valve in A-V discordance (**di**) extending into double inlet univentricular heart of right ventricular type with straddling right valve (**dii**). The hearts can alternatively be grouped into those with a primary chamber of right ventricular type (**a** and **d**) and those with a primary chamber of left ventricular (LV) type (**b** and **c**). The **diagonal hatching** indicates a chamber of right ventricular morphology and the **vertical hatching** a chamber of left ventricular morphology.

TABLE I

Segmental Connections and Details of Hearts With Two Valves, One of Which Straddled Into a Primary Chamber of Right Ventricular Morphology (18 cases)

Connections	no. of Cases	Ventricular Morphology	% of Override to 1° Chamber
A. With Left Ventricular Secondary Chamber to Left and With Straddling Left Valve (12 cases)			
Solitus-concordant-concordant	4	Biventricular	10–20
Solitus-concordant-DORV	7	Biventricular	0–45
Solitus-double inlet-DOPC	1	Univentricular	85
B. With Right Ventricular Secondary Chamber to Right and With Straddling Right Valve (4 cases)			
Solitus-discordant-discordant	1	Biventricular	20
Solitus-discordant-DORV	2	Biventricular	20, 45
Solitus-discordant-single outlet*	1	Biventricular	45
C. With Right Ventricular Secondary Chamber to Right and With Straddling Left Valve (criss-cross hearts, 2 cases)			
Solitus-double inlet-single outlet*	2	Univentricular	80

* = Hearts with single outlet all had pulmonary atresia; 1° = primary.
DOPC = double outlet from primary chamber; DORV = double outlet right ventricle

identified within the triangle of Koch in the atrial septum and the penetrating bundle descended posteriorly onto the septum extending to the crux.

Straddling right valve and right-sided secondary chamber: Four hearts in this category were examined (Table I), all again from patients with situs solitus. The morphologic features of the straddling valve were again those of a mitral valve, and the valve straddled the anterior part of the septum. These hearts have been described in detail elsewhere.[21] The degree of override was such that all the hearts were biventricular with A-V discordance. In all hearts the septum again extended to the crux cordis and its external site was marked anteriorly by an anterior descending branch from the right coronary artery and posteriorly by the posterior descending coronary artery. The secondary chamber always possessed a trabecular zone of left ventricular type and its dimensions related to the degree of overriding of the straddling valve. The conducting tissues were examined in three of the hearts, and have also been previously described.[21] Two of the hearts had anterolateral connecting A-V nodes, the penetrating bundle descending directly onto the anterior limb of the septum and being unrelated to the ventricular outflow tracts; the third heart possessed a sling of conduction tissue.

Straddling left valve and right-sided secondary chamber: Two hearts in this category were examined (Table I). The basic anatomy of the hearts was similar

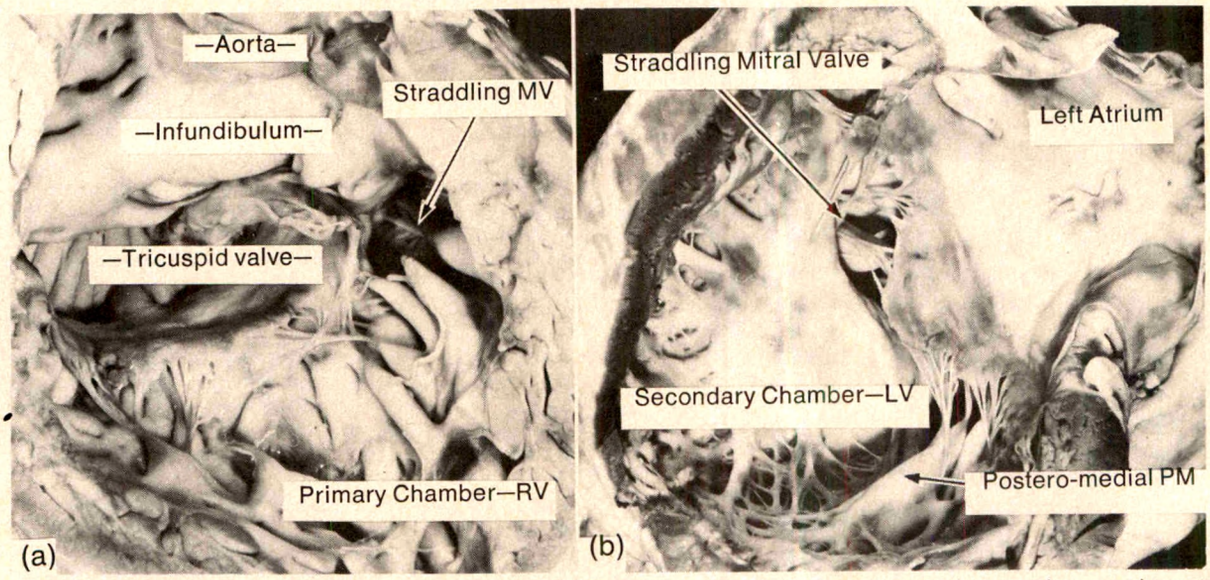

FIGURE 4. Photographs illustrating the morphologic features of a straddling mitral valve (MV) in the setting of A-V concordance. **a,** shows the right ventricular (RV) aspect and **b,** the left ventricular (LV) aspect. PM = papillary muscle.

to that found in the univentricular heart with a right ventricular primary chamber and left-sided rudimentary chamber except that rotation of the heart had carried the rudimentary chamber to a right-sided position. The hearts were therefore criss-cross hearts with straddling of the left A-V valve. In both hearts the straddling valve was committed by 80 percent to the primary chamber, and the arterial connection was single outlet from the primary chamber with pulmonary atresia. The conduction tissues were not studied histologically in these hearts but examination of the gross specimens suggested that the ventricular conduction tissues would take origin from a regular A-V node because, despite the rotation of the heart, the septum still extended to the crux and was aligned with the atrial septum.

Primary chamber of left ventricular morphology: *With straddling left valve and left-sided secondary chamber:* Segmental details of the 11 individual hearts falling into this cateogry are shown in Table II. In each heart the straddling valve was morphologically a tricuspid valve. The degree of override was such that four hearts were biventricular with A-V discordance and seven hearts univentricular with double inlet to the primary chamber of left ventricular morphology. In none of these hearts did the septum extend to the crux cordis. The precise point of contact of its posterior limb with the A-V junction varied between the obtuse point and the crux, being more anterior in the cases with double inlet. In all the hearts the valve straddled the posterior part of the septum. One of the hearts had the rudimentary chamber almost directly anterior but with its trabecular zone pointing to the right. Otherwise it resembled the double inlet hearts with left-sided rudimentary chambers and has therefore been included in this group. The site of the anterior limb of the septum was marked by a descending branch from the right coronary branch in most of the cases and the posterior

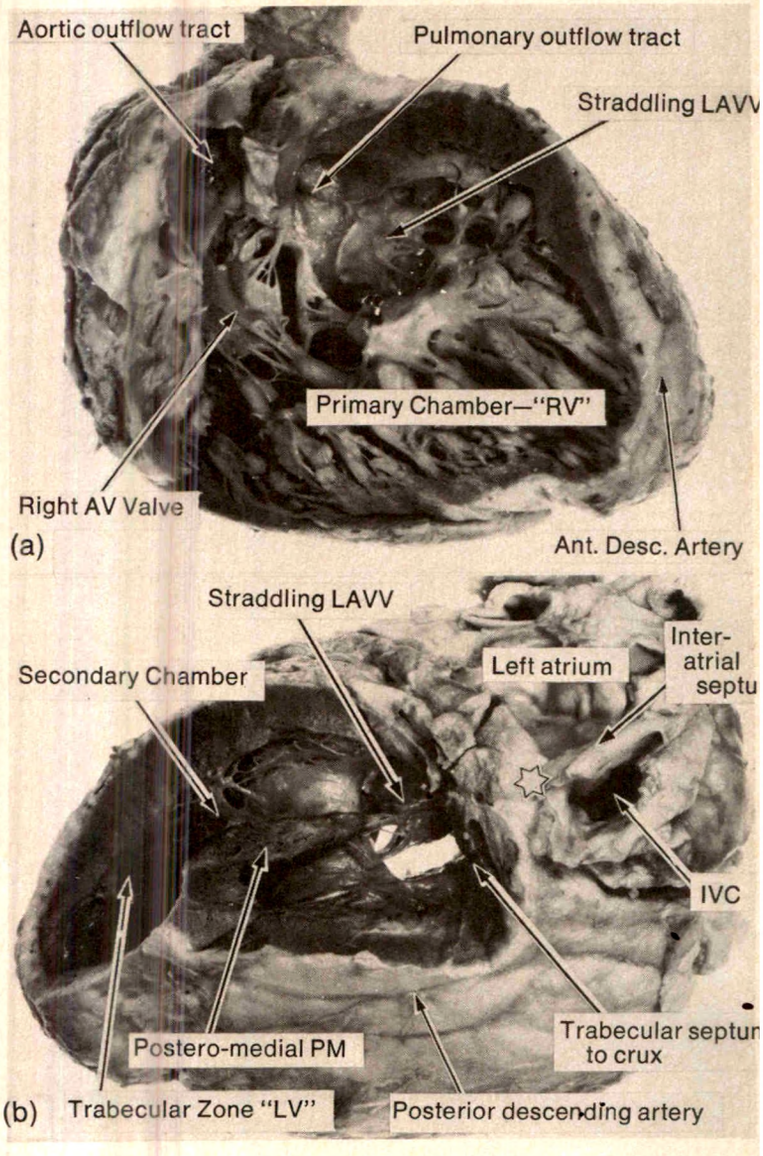

FIGURE 5. Photographs illustrating the morphologic features of a straddling left atrioventricular (AV) valve (LAVV) in the setting of a double inlet ventricle of right ventricular (RV) morphology with a posterior left-sided rudimentary chamber of left ventricular (LV) type. **a,** shows the primary chamber aspect and **b,** the secondary chamber of unequivocally left ventricular morphology. Note the septum extending to the crux (**star**). Ant. Desc. = left-anterior descending coronary; IVC = inferior vena cava; PM = papillary muscle.

TABLE II

Segmental Connections and Details of Hearts with Two Valves, One of Which Straddled Into a Primary Chamber of Left Ventricular Morphology (28 cases)

Connections	no. of Cases	Ventricular Morphology	% of Override to 1° Chamber
A. With Right Ventricular Secondary Chamber to Left and With Straddling Left Valve (10 cases)			
Inversus-concordant-discordant	1	Biventricular	40
Solitus-discordant-discordant	3	Biventricular	10–45
Solitus-double inlet-discordant	6	Univentricular	60–95
B. With Right Ventricular Secondary Chamber to Left and Straddling Right Valve (1 case)			
Solitus-double inlet-discordant	1	Univentricular	90
C. With Right Ventricular Secondary Chamber to Right and Straddling Right Valve (17 cases)			
Solitus-concordant-concordant	4	Biventricular	30–45
Solitus-concordant-discordant	2	Biventricular	35, 45
Solitus-concordant-DOLV	1	Biventricular	5
Solitus-double inlet-concordant	3	Univentricular	55–60
Solitus-double inlet-discordant	6	Univentricular	70–100
Solitus-double inlet-DOPC	1	Univentricular	80

DOLV = double outlet left ventricle; other abbreviations as in Table I.

limb by a descending branch of the left coronary artery. However, the artery delimiting the posterior limb was not the posterior descending coronary artery. The latter structure was poorly formed but descended into the diaphragmatic ventricular surface at the crux, not marking a septal structure. As in the hearts with a left ventricular secondary chamber, the right ventricular secondary chambers in these hearts with left ventricular primary chambers all possessed discrete trabecular zones, the degree of development of the trabecular zones being correlated with the degree of override of the straddling valve.

Gross examination of the smooth "left ventricular" septal surface of these hearts suggested an anterior A-V conduction system. Histologic study in one heart confirmed the suspicion, the A-V bundle originating from a node situated anterolaterally in the right A-V orifice (Fig. 6). The bundle encircled the pulmonary outflow tract from the primary ventricular chamber to reach the anterior limb of the septum, giving an overall view similar to that seen either in congenitally corrected transposition[22] or in univentricular hearts of the left ventricular type and left-sided rudimentary chamber.[23]

With straddling right valve and right-sided secondary chamber: The segmental arrangement and associated anomalies of the 17 hearts identified in this category are tabulated in Table II. In all hearts the straddling valve was morphologically tricuspid except in three hearts with double inlet in which the straddling valve was morphologically indeterminate. In seven hearts the straddling valve opened by its larger part to the secondary chamber, the hearts being biventricular with A-V concordance. The other 10 hearts, in which the straddling valve drained for its most part to the primary chamber, were considered univentricular hearts of left ventricular type with double inlet. Irrespective of the degree of override none of the hearts possessed a septum extending to the crux cordis (Fig. 7). In the univentricular hearts the septum extended to the anterolateral quadrant of the right orifice, whereas in the biventricular hearts it ran into the posterolateral quadrant. In the latter hearts the septum was therefore closer to the crux, but it was never orientated in line with the atrial septum because of the presence of the straddling valve, which always straddled the posterior part of the septum. As with the other categories, the size of the trabecular component of the secondary chamber was larger in the biventricular specimens than in the univentricular hearts.

Examination of the specimens suggested presence of the conducting tissues on the posterior limb of the septum. Histologic examination in one biventricular and two univentricular specimens confirmed this distribution and showed that the penetrating bundle ran up the posterior limb of the septum and made contact with a node in the parietal part of the right A-V junction (Fig. 7). This was *not* the regular A-V node, this structure being situated in its anticipated site in the triangle of Koch but not making contact with the ventricular myocardium. However, in all three hearts the connecting A-V node was *posterior* in position relative to the regular node (Fig. 7). In one heart another hypoplastic anterior node was identified but, like the regular node, it made no contact with ventricular myocardium. In most of the hearts the limbs of the septum between primary and secondary chambers were marked externally by descending branches from right and left coronary arteries, the right descending artery dipping onto the septum at various points around the junction depending on the degree of straddling of the valve. An artery was usually found descending onto the diaphragmatic surface of the primary chamber at the crux, but this did not mark the site of any septal structure. However, a well formed posterior ridge was found in the primary chamber at this site, being particularly well

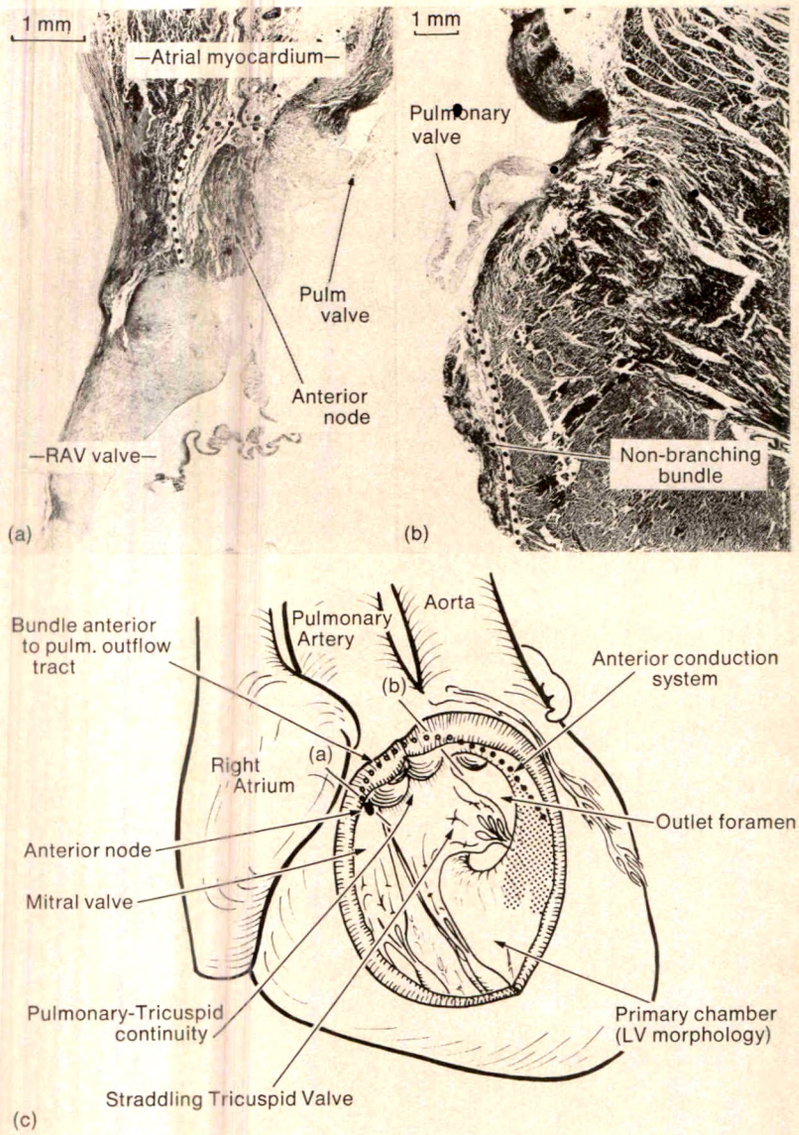

FIGURE 6. Illustration of the conduction tissue from a heart with a primary chamber of left ventricular (LV) type and left-sided secondary chamber with straddling of the left atrioventricular [A-V] valve. **a,** shows a section of the anterior node and **b,** the anterior nonbranching bundle. The position of these structures is shown in **c,** an artist's impression of the main chamber aspect of the conduction system. Note the position of the bundle anterior to the pulmonary (pulm.) outflow tract. RAV = right A-V valve.

developed in the univentricular hearts. In no heart did it carry any conduction tissues.

Hearts with straddling common valves: Seven hearts were examined with a common valve that was unequally committed between the chambers in the ventricular mass (Table III). All were considered to be univentricular with double inlet connection by way of the common valve. In all respects they were comparable with the hearts already described except that the straddling valve was common to both atrial chambers.

Hearts with both valves straddling: Two hearts were examined in which both the right and left A-V valves straddled the septum. In both, the right-sided chamber was anterior and had a right ventricular trabecular pattern, the posterior left-sided chamber being morphologically a left ventricle. In neither heart did the septum extend to the crux. The tricuspid valve overrode the posterior part of the septum, about 20 percent straddling into the left ventricle in one heart and 5 percent in the other while 5 percent of the mitral valve overrode the anterior septum into the right ventricle in both hearts. The arterial connection in both was discordant. These hearts are so unusual that a detailed description of their morphologic features will be given elsewhere (in preparation).

Overriding Valves Without Straddling

Two hearts were examined in which the valve orifice was related to both chambers while its tension apparatus was entirely located within one ventricular chamber. In one heart with situs solitus, both ventricular inlet portions were connected to a main ventricular chamber of the left ventricular type, but the orifice of the right valve, attached by its inferior commissure to the septum, pointed like a keyhole into the anterior rudimentary chamber of a right ventricular type (Fig. 8). The secondary chamber was anterior and right-sided,

and supported both great arteries. It was delimited to either side by descending branches from the right and left coronary arteries.

The other heart was a biventricular heart with situs solitus, A-V concordance and all the stigmata of an A-V defect ("A-V canal malformation"). Thus the ventricular inlet dimensions were considerably less than the outlet dimensions, and the aortic outflow tract was elongated and right-sided. Nonetheless, the atrial septum was intact and there were discrete mitral and tricuspid orifices. There was an extensive perimembranous ventricular septal defect that excavated the inlet septum toward the crux, but that septum aligned with the atrial septum. The A-V conduction system took origin from a regular node, but the whole system was displaced posteriorly as is usual in A-V defects. Although all the tension apparatus of the tricuspid valve was contained within the morphologically right ventricle, the anterosuperior margin of its orifice extended through the perimembranous defect and drained to the left ventricle.

Discussion

Hearts with straddling atrioventricular (A-V) valves are a problem. For the physician they frequently lead to diagnostic difficulties. For the surgeon they may create challenging if not insuperable operative problems.[24] They also present a problem for the morphologist, especially if he is bold enough to attempt to classify them. Surprisingly, their recognition is a relatively recent event. The earliest description of a straddling A-V valve (excluding common valves) of which we are aware is that of Lambert.[2] Neufeld et al.[25] in their study of ventricular septal defects also illustrated the lesion, but they did not nominate the valves as straddlers. The close association between hearts with straddling valves and

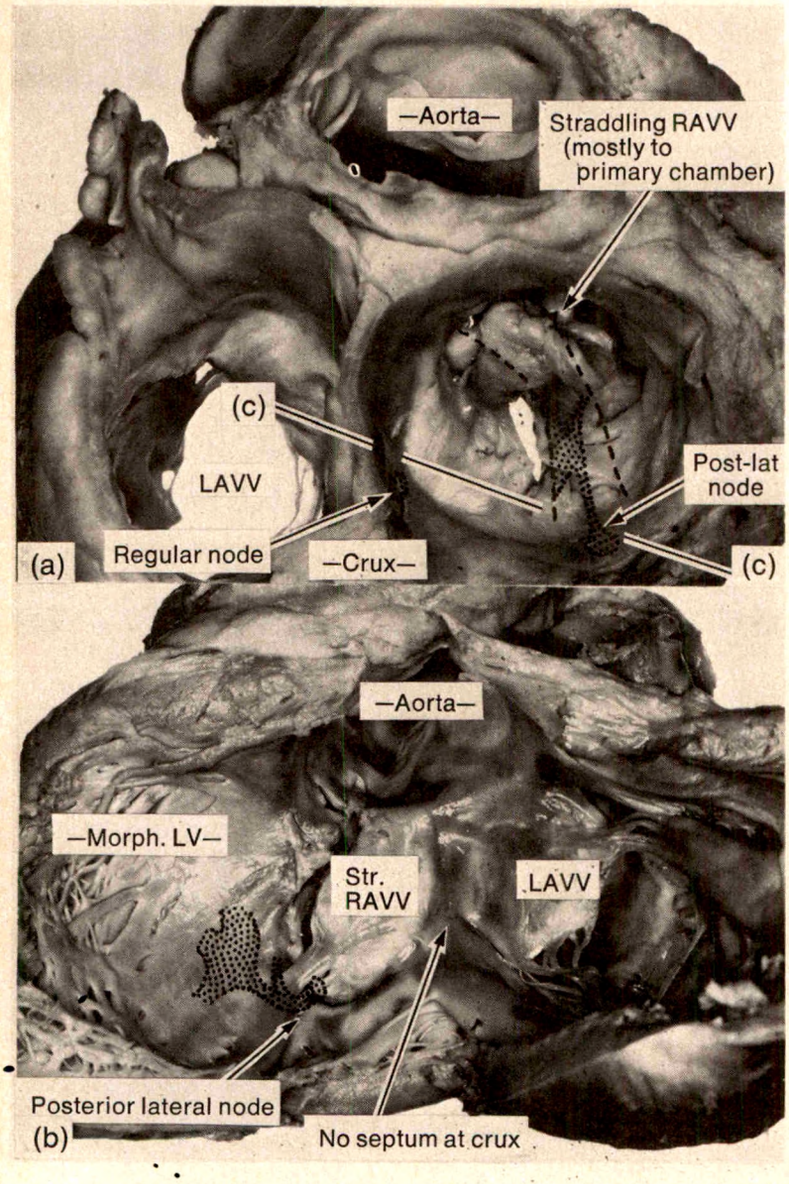

FIGURE 7. Photographs of a heart with straddling right (atrioventricular [A-V]) valve (RAVV) in the setting of double inlet and a primary chamber of left ventricular type (LV) with a right-sided secondary chamber of right ventricular type. **a,** shows the dissected A-V junctions viewed from above. Note that the straddling valve is committed more to the primary than to the secondary chamber (double inlet A-V connection). The septum (**dotted lines**) does not reach to the crux. The conduction tissues have been superimposed. **b** shows the primary chamber aspect of the straddling (STR) valve with superimposition of the conduction tissues. Note that there is no septum at the crux. LAVV = left atrioventricular valve; Morph. = morphological; Post.-lat = posterolateral.

TABLE III

Segmental Connections and Details of Hearts With Unequal Commitment of a Common Atrioventricular Valve (7 cases)

Connections	no. of Cases	Ventricular Morphology	Position of 2° Chamber	% of Override to 1° Chamber
Solitus-double inlet-DOPC	2	UVH-"RV"	Left, posterior	90%
Solitus-double inlet-concordant	2	UVH-"LV"	Right, anterior	90%
Inversus-double inlet-single outlet*	1	UVH-"LV"	Left, anterior	95%
Ambiguous-double inlet-concordant	1	UVH-"LV"	Right, anterior	95%
Ambiguous-double inlet-DOPC	1	UVH-"RV"	Right, posterior	95%

* Single outlet with pulmonary atresia.
DOPC = double outlet primary chamber; 1° = primary; 2° = secondary; UVH-"LV" = univentricular heart with primary chamber of left ventricular morphology; UVH-"RV" = univentricular heart with primary chamber of right ventricular morphology.

univentricular hearts was subsequently highlighted by several authors,[4,13] but the most detailed investigations were that of Liberthson et al.[1] on the left ventricular type and that of Quero-Jimenez et al.[6] concerning the right ventricular variety. Despite these investigations, and the recent surge of interest following the recognition of the value of echocardiography in diagnosis,[9–12] there is no consensus on the optimal method of categorizing these malformations.[1,4,6,7,25,26]

Classification of Straddling Valves

Our investigation has shown that right, left or common A-V valves can straddle a septum in the presence of all chamber combinations possible in the patient with a situs solitus heart. We have also observed two hearts in which both valves straddled and yet other hearts in which a valve straddled in the absence of one A-V connection (valve atresia). The latter anomaly has been described previously,[1,14,15] but we excluded from this presentation the hearts of this type that we examined in the interests of clarity and brevity. In the hearts we included in our study definite patterns of malformation were recognizable.

Straddling right A-V valve: We found that the straddling right valve could be either a morphologic tricuspid valve or a morphologic mitral valve. When in a situs solitus heart the valve was morphologically tricuspid we found that it always straddled the posterior

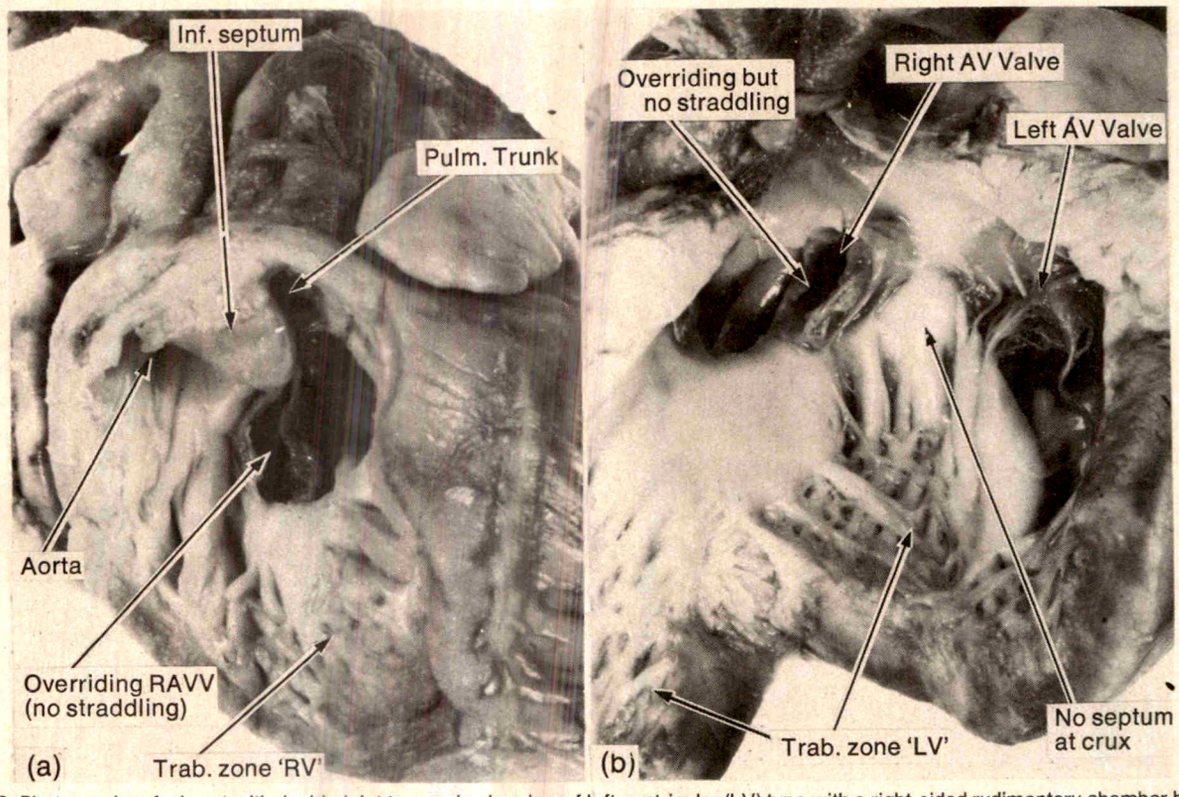

FIGURE 8. Photographs of a heart with double inlet to a main chamber of left ventricular (LV) type with a right-sided rudimentary chamber but with overriding of the right atrioventricular (AV) valve (RAVV) to the rudimentary chamber in the absence of straddling. **a** shows the rudimentary chamber aspect and **b**, the main chamber aspect. Inf. = infundibular; Pulm. = pulmonary; Trab. = trabecular.

part of a septum that never extended to the crux in a heart with a primary chamber of left morphologic features and a secondary chamber of right morphologic features, the secondary chamber always being anterior and right-sided. In contrast, when the straddling right valve was morphologically mitral in a situs solitus heart it always straddled the anterior part of a septum that did extend to the crux in a heart with a primary chamber of right ventricular morphology and a right-sided secondary chamber of left morphology.

Straddling left A-V valve: In similar fashion we found that a straddling left valve could be either mitral or tricuspid in morphology. As with the right valve, when the straddling left valve was a mitral valve it always straddled the anterior part of a septum that extended to the crux in a heart with a right ventricular main chamber and a left ventricular secondary chamber, the secondary chamber being left-sided and posterior except in two criss-cross hearts where it was right-sided and posterior. When the straddling left valve was tricuspid, it always straddled the posterior part of a septum that never extended to the crux in a heart with a left ventricular main chamber and an anterior secondary chamber that was always left-sided and anterior except in a single case in which its trabecular zone extended to the right. Thus there were four basic chamber and valve combinations associated with straddling that can simply be considered as the mitral or tricuspid valves straddling in the settings of either A-V concordance or A-V discordance.

Double inlet ventricle versus A-V concordance or discordance: Our studies have further shown that the degree of commitment of the straddling valves does not always determine the A-V connections of concordance or discordance. In many hearts the orifice of the straddling valve was committed in almost its entirety to the primary ventricular chamber. In these hearts, therefore, the connection could be considered as double inlet ventricle. Furthermore, our study showed that a series of hearts existed between the connections of double inlet and concordance or discordance in each of the four patterns of straddling recognized (Fig. 3). So, in order to categorize the A-V connection in all of these series we took as the dividing point between double inlet and either concordance or discordance the stage at which more than 50 percent of the overriding valve opened into the primary ventricular chamber. Although the purpose of this convention was simply to categorize the A-V connection, it does have implications for the terminology of the ventricular chambers. It is accepted by many authors[17,27,28] that a major criterion for "single ventricle" is the presence of a double inlet connection. When, therefore, hearts in our series had a double inlet connection we categorized them as univentricular hearts with straddling valves and described their constituent chambers accordingly as the ventricle and a rudimentary chamber, respectively.

Anular versus peripheral straddling (overriding versus straddling): The precedent for our division of a series of anomalies characterized by overriding of a valve anulus exists in the treatment of overriding arterial valves by Kirklin et al.[17] so as to avoid the necessity for creation of an intermediate category. Our study suggests that this concept works with equal facility for overriding A-V valves. But further refinement is necessary in the case of A-V valves because they have a tension apparatus in addition to an anulus and leaflets. The fact that anulus and tension apparatus could "straddle" independently was recently recognized by Bharati et al.[29] and they described these two facets as anular straddling and peripheral straddling, respectively. We prefer to distinguish them by terming the former overriding and reserving the term straddling for description of the situation when the tension apparatus is attached to both sides of a septum, as also suggested recently by Tabry et al.[24] Almost always a valve will both straddle and override in these terms, but our investigation has demonstrated that a valve can straddle without overriding or more rarely can override without straddling. It is the degree of override which determines the atrioventricular connection present.

In both their earlier study[1] and their more recent abstract,[29] Lev's group described yet another group of malformations, namely, those with "displaced" valves. This term describes hearts with double inlet in which the rudimentary chamber has such a well formed trabecular zone that it gives the appearance of a normal ventricular "sinus." However, in our experience,[30] hearts with double inlet always have rudimentary chambers that possess a trabecular zone, although it is rarely large enough to mimic the trabecular zone of a normal ventricle. Nonetheless, by describing both the connection and the size of the rudimentary chamber we have no need to create a separate category for "displaced" valves.

Do Common A-V Valves Straddle?

These considerations are also pertinent to the controversy concerning common A-V valves. Liberthson et al.[1] excluded such hearts from the category of straddling valves for semantic reasons while agreeing that they fulfilled the criteria for straddling. Thus they commented that "conceptually some of them belong to this group."[1] We consider a common A-V valve a valve that drains both atrial chambers to the ventricular mass. Such a valve does not always have its tension apparatus attached to both sides of a septum; for example, common valves are known to drain both atria exclusively to the same ventricular chamber.[27,28] Nevertheless, in the majority of hearts with a common valve the valve is committed approximately equally to both chambers. The valve tension apparatus arises in these hearts to both sides of the ventricular septum; thus, within our terminology, it straddles (Fig. 2).

There are positive advantages to be gained from recognizing common valves as straddling because, as shown in this investigation and as recognized by Liberthson et al.,[1] such valves can present problems identical to those posed by straddling left or right valves. Thus with any straddling valve it is important to consider both its nature (that is, right, left or common) and its commitment to the chambers in the ventricular mass

(that is, its degree of override). Although the "cut-off" point for determination of the connection of a straddling right or left valve is 50 percent, an unequally committed common valve cannot be separated in terms of its connection at the 50 percent point. This is because the common valve by definition drains both atria. If one side of a common valve together with its atrium and ventricle are hypoplastic[19] we would take this into account when determining the A-V connection. It is only when a common orifice without hypoplasia of its right or left component is unequally committed between the ventricular chambers that a 75 percent rule is necessary. We have rarely needed to invoke this rule because the orifice is usually almost entirely committed to the primary chamber with minimal straddling of chordae from the rudimentary chamber.

Surgical Implications

Role of the conduction system: The recognition of the patterns we have noted of straddling valves has important surgical implications because the disposition of the conduction tissues varies depending on the pattern of straddling valve. When the heart has a left ventricular primary chamber, the septum never extends to the crux whether the secondary chamber is right- or left-sided or whether the heart is univentricular or biventricular. Therefore the conduction tissues will not arise from the regularly situated A-V node. When the heart is univentricular, this finding is not unexpected, because the connecting node is known to be anterior in these hearts irrespective of the position of the rudimentary chamber.[23,31,32] When the heart is biventricular and the secondary chamber is left-sided, the hearts represent corrected transposition with straddling tricuspid valve. Again, therefore, the node may be anticipated to be anterior.[23] However, it is perhaps a little surprising to find the node unusually situated when the biventricular heart with "normally related" chambers has a straddling tricuspid valve. The important finding in these hearts is that the septum does not extend to the crux, and therefore does not fulfill the criteria for formation of a normally located conduction system.[33] For this reason, it is perhaps misleading to refer to the ventricular septal defect in the presence of "normally related" chambers and a straddling tricuspid valve as an "A-V canal defect."[5,25,34] The characteristic feature of an A-V canal defect is that the septum, although hypoplastic and scooped out, does run to the crux. In this heart, the conduction tissue did originate from a regular node despite the overriding tricuspid valve because the septum extended to the crux. In contrast, in hearts with A-V concordance and *straddling* tricuspid valves, our experience indicates that the connecting A-V node is not the regular node in the atrial septum. Thus, the problem confronting the surgeon is not the same as with the perimembranous inlet defect that "scoops out" the septum towards the crux. This feature highlights the possible difficulties engendered by usage of the term "isolated A-V canal ventricular septal defects." It is our belief that, if the term is used at all, it should be reserved for perimembranous inlet defects in hearts with separate mitral and tricuspid valves but the other stigmata of A-V defects. It seems both inappropriate and potentially misleading to use the term to describe the defect in A-V concordance with a straddling tricuspid valve.

In contrast to straddling valves in hearts with a left ventricular primary chamber, the conduction tissues do vary depending on the type of valve straddling when the primary chamber is of right ventricular morphology. When the secondary chamber of left ventricular morphology is to the left, the conduction tissue originates from a regular node whether the A-V connection is concordant or of the double inlet type. The most vulnerable part of the defect is the posterior ascending limb of the septum at its fusion point with the A-V junction, this being the site of the penetrating bundle. In contrast to this regular position of conducting tissue with a straddling left valve and a left-sided secondary chamber, the A-V bundle in hearts with a straddling right valve and a right-sided secondary chamber originates from an anterior node, as in corrected transposition, or else forms a conduction tissue sling. The special problems produced by these arrangements are discussed elsewhere.[21]

Possible surgical techniques and risks to the conduction system: The surgeon attempting repair of a heart with a straddling valve has several possible techniques at his disposal.[24] If he is to avoid valve replacement it is likely that repair will involve patching or septation within the primary chamber in order to restore to the secondary chamber the straddling inlet portion. In this context, the only heart likely to have conduction tissue related to the posterior quadrant of the patch at the crux is the right ventricular type. In hearts with left ventricular primary chambers, our observations suggest that the crux will be free of conduction tissue, but it would be a wise precaution to test this hypothesis by intraoperative mapping. Other options open to the surgeon are replacement of the straddling valve with a prosthesis, or closure of a straddling right valve and utilization of a modified Fontan procedure. Both procedures are likely to place the conduction tissue at risk, and if the right valve is to be replaced then the likelihood of an unusually situated node must be kept in mind. Furthermore, if a right-sided secondary chamber is to be used as part of the pulmonary circuit in the Fontan procedure, necessitating closure of the septal defect, the penetrating bundle is likely to be at high surgical risk. Its precise position should therefore be identified, ventricular morphology giving an excellent guide to its site.

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Positional Abnormalities of Atrioventricular Valves in Transposition of the Great Arteries Including Double Outlet Right Ventricle, Atrioventricular Valve Straddling and Malattachment

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Positional abnormalities (straddling or overriding) of the atrioventricular (A-V) valves were studied using angiographic, sector scan echocardiographic and postmortem anatomic data in 10 patients with transposition of the great arteries including double outlet right ventricle. Group I included six patients with tricuspid valve abnormalities. This group was further classified into: (a) patients with anular straddling and abnormal attachment of portions of the tricuspid leaflets in the left ventricle (malattachment) or on the ventricular septum, or both (four patients with d-transposition of the great arteries and hypoplastic right ventricle); and (2) patients with malattachment of portions of the tricuspid valve leaflet to the crest or left ventricular surface of the septum (septal malattachment) without significant anular straddling (two patients with d-transposition of the great arteries).

Group II included four patients with mitral valve abnormalities without significant anular straddling, further classified into: (1) patients with septal malattachment of the portions of the mitral valve to the crest and right ventricular surface of the ventricular septum (two patients with double outlet right ventricle); and (2) patients with ventricular malattachment of portions of the mitral valve leaflets to the papillary muscles in the right ventricle (two patients with ventricular septal defect and discordant criss-cross atrioventricular connections).

On the basis of these observations and reported experience, two main types of positional abnormalities of the A-V valves were recognized: (1) anular straddling in which the A-V anulus straddled the ventricular septum above the contralateral ventricle, together with ventricular leaflet malattachments, and (2) leaflet malattachment of either the septal or ventricular type without significant straddling of the valve anulus. Angiocardiography and sector scan echocardiography helped to identify these abnormalities of the A-V valves.

Advances in surgical technique have now made it possible to undertake intracardiac correction of complicated forms of transposition of the great arteries including double outlet right ventricle with ventricular septal defect by a variety of methods. Selection of the most suitable operation requires accurate preoperative diagnosis of the atrioventricular (A-V) and ventriculoarterial (V-A) connections, the relative sizes of the ventricles and the alignment and attachment of the A-V valves to their respective ventricles. Within the spectrum of various forms of transposition and double outlet right ventricle malformation, positional abnormalities of the A-V valves are not frequent. Liberthson et al.[1] have described the pathologic spectrum of straddling for both the tricuspid and mitral valves in various types of transposition.

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In the past the term straddling of the A-V valve orifices has been applied to hearts either with overriding of the valve anulus across the interventricular septum and partial insertion of portions of the leaflet apparatus into the contralateral ventricle, or without significant overriding of the valve anulus[1–7] but with insertion of portions of the leaflet apparatus to the crest or contralateral surface of the interventricular septum or to the papillary muscles in the contralateral ventricle, or both. Until recently, no definite distinction was made between these two types. Because the situation in which only the leaflet apparatus is displaced with malattachment to the ventricular septum is not strictly a form of straddling, we have used the term malposition of the A-V valves to include all forms of positional abnormalities of the various components of the valve apparatus in relation to its corresponding ventricle. Straddling defines the situation in which the valve anulus is displaced in relation to the ventricular septum and overrides the ventricular septum across the ventricular septal defect and there are abnormal attachments of portions of the leaflet apparatus to the papillary muscles or ventricular septum in the contralateral ventricle, or both. Malattachment is defined in the situation in which no significant anular straddling is present, and portions of the leaflet apparatus are attached to the crest or left ventricular surface of the ventricular septum (septal malattachment) or in the

TABLE I

Clinical Data of 10 Patients With Atrioventricular Valve Malposition

Case no.	Age (yr)	Diagnosis	PS Valve	PS Subvalve	RV Size	A-V Valve Malposition: Tricuspid An Strd	Tricuspid Mal Sept	Tricuspid Mal Vent	Mitral An Strd	Mitral Mal Sept	Mitral Mal Vent	ECG QRS Axis	ECG Vent Hypertrophy	Surgery	Follow-Up Data
						Group I-1									
1	3.3	d-TGA, VSD, po PAB	−	−	Hypo	+*	+	+	NL	NL	NL	LAD	LVH	Exploration,* septectomy	Died, PVO
2	12.0	d-TGA, VSD, po PAB	−	−	Hypo	+	−	+	NL	NL	NL	LAD	LVH	None	Alive
3	11.0	d-TGA, VSD	+	−	Hypo	+	−	+	NL	NL	NL	LAD	LVH	None	Alive
4	4.5	d-TGA, VSD	+	+	Hypo	+*	−	+	NL	NL	NL	RAD	RVH	Exploration,* septectomy	Alive
						Group I-2									
5	8.3	d-TGA, po Blalock-Taussig	−	+	Large	−	+*	−	NL	NL	NL	LAD	RVH	Mustard, VSD closure, LVOTS resection	Alive
6	16.0	l-TGA, VSD, po Cooley shunt	−	+, pulm atresia	Small	−	+*	−	NL	NL	NL	RAD	RVH	None	Died, septicemia
						Group II-1									
7	17.5	Taussig-Bing, po PAB	−	−	Large	NL	NL	NL	−	+*	−	?	LVH	Mustard, VSD closure	Died, unrelieved LVOTS
8	11.0	Taussig-Bing	−	−	Large	NL	NL	NL	−	+*	−	RAD	RVH	Mustard, VSD closure, LV-PA valved conduit	Alive
						Group II-2									
9	7.0	Criss-cross, l-loop, l-TGA, VSD, po Cooley shunt	−	+, pulm atresia	Large	NL	NL	NL	−	−	+*	RAD	RVH	VSD closure, MV prosthesis, LV-PA conduit	Died
10	16.0	Criss-cross, l-loop, l-TGA, VSD, po Blalock-Taussig shunt	−	+	Large	NL	NL	NL	−	−	+	RAD	RVH	None	Alive

* Echocardiographic and angiographic diagnosis confirmed intraoperatively or at autopsy.

An = anular; A-V = atrioventricular; d-TGA = complete transposition of the great arteries; ECG = electrocardiogram; Hypo = hypoplastic; LAD = left axis deviation; l-TGA = l-transposition of the great arteries; LV = left ventricle; LVH = left ventricular hypertrophy; LVOTS = left ventricular outflow tract stenosis; Mal = malattached; MV = mitral valve; NL = normal; PA = pulmonary artery; PAB = pulmonary arterial banding; po = postoperative; PS = pulmonary stenosis; pulm = pulmonary; PVO = pulmonary venous obstruction; RAD = right axis deviation; RV = right ventricle; RVH = right ventricular hypertrophy; Sept = septal; Strd = straddling; Vent = ventricular; VSD = ventricular septal defect. + = present; − = absent; ? = indeterminate.

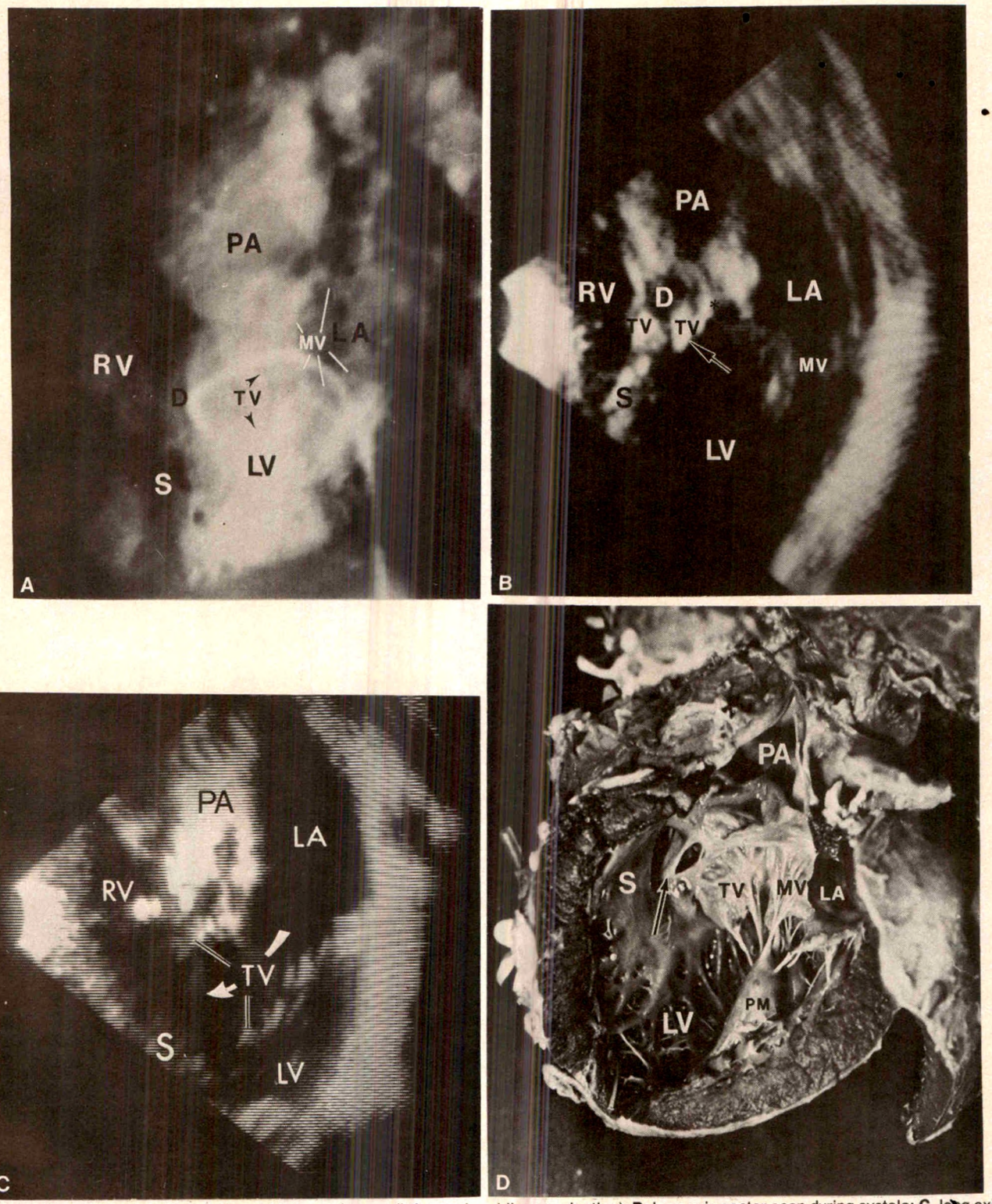

FIGURE 1. Case 1 (Group I-1). **A**, left ventricular angiogram (left anterior oblique projection); **B**, long axis sector scan during systole; **C**, long axis sector scan during diastole; **D**, postmortem specimen. d-transposition of the great arteries is present, and the right ventricle (RV) is hypoplastic. The tricuspid valve anulus (**arrows in A, B, C and D**) is seen to straddle the ventricular septum (S) across the ventricular septal defect (D) and is displaced into the left ventricle (LV). Note the confluence (**asterisk**) of the tricuspid (TV) and mitral (MV) valve leaflets in **B.** In **C** and **D** note that the papillary muscle (PM) in the left ventricle has malattachments from a portion of the straddling tricuspid valve and normal attachments from the mitral valve leaflet apparatus.

contralateral ventricle (ventricular malattachments). Lesions with a common A-V canal defect are excluded from this discussion.

The identification of great vessels and ventricular chambers and their location and size can reliably be assessed with angiography. In contrast, the A-V valves are often inadequately visualized and only subtle contrast outlines of the A-V orifices indicate their relative position and flow patterns. With new sector scanning echocardiographic techniques it is now possible to visualize the A-V connections noninvasively as well as to evaluate the relative sizes of the ventricles and define ventriculoarterial relation.[8–10]

The purposes of this study were (1) to correlate the clinical, angiographic, echocardiographic and anatomic spectrum of positional abnormalities of the tricuspid and mitral valves in patients with various forms of transposition of the great arteries or double outlet right ventricle, and (2) to characterize the spectrum of positional abnormalities of various components of A-V valve apparatus.

Methods

Patients: Ten patients aged 3.3 to 16 years (mean 9.9) were included in the study (Table I). Group I included six patients with malposition of the tricuspid valve apparatus. Group I was further classified into: Group I-1, straddling tricuspid valve anulus and malattachment of portions of the tricuspid valve leaflets into the left ventricle—four patients with hypoplastic right ventricle, d-transposition of the great arteries and ventricular septal defect (S,D,D); and Group I-2, normally located tricuspid valve anulus with malattachment of the tricuspid valve leaflet to the rim of the ventricular septal defect—two patients, one with d-transposition of the great arteries, enlarged right ventricle, ventricular septal defect and left ventricular outflow tract stenosis (S,D,D) and one with l-transposition of the great arteries, superoinferior ventricles, mod-

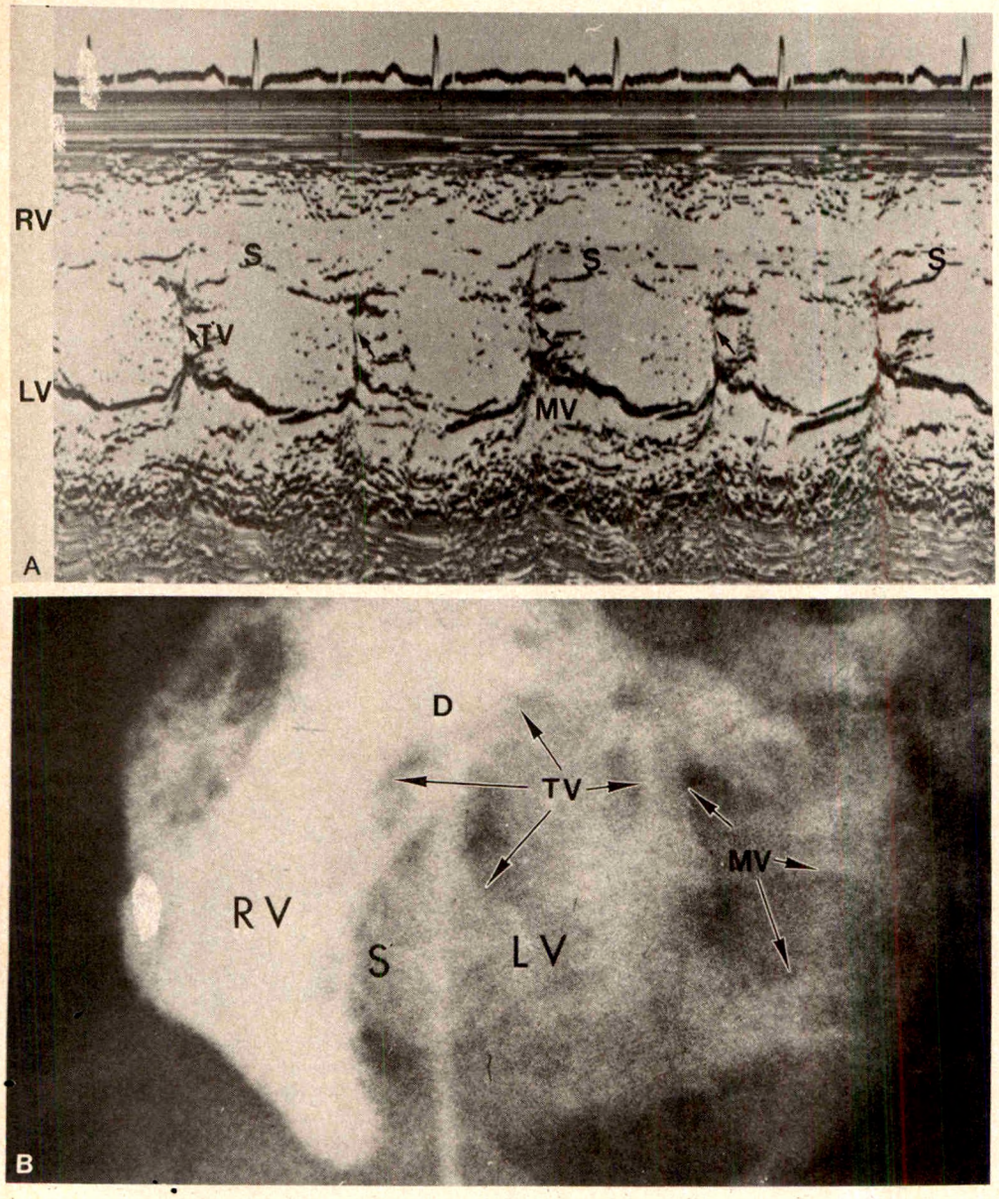

FIGURE 2. Case 3 (Group I-1). **A**, M mode left ventricular echocardiogram. The right ventricle (RV) is small and the interventricular septum (S) is distinct. Both the tricuspid (TV) and mitral (MV) valves are located in an enlarged left ventricle (LV). During diastole the septal leaflet of the tricuspid is seen to course through the ventricular septal defect into the right ventricle (**arrow**). **B**, right ventricular angiogram (left anterior oblique view) confirms the presence of a relatively hypoplastic right ventricle (RV), ventricular septal defect and straddling tricuspid valve anulus (**arrows**) observed in the echocardiogram.

erately hypoplastic superior right ventricle, ventricular septal defect and pulmonary atresia (S,L,L).

Group II included four patients with malattachment of the mitral valve apparatus and normally located mitral valve anulus. Group II was further classified into: Group II-1, septal malattachment of the portions of the mitral valve leaflets to the rim of the ventricular septal defect—two patients with double outlet right ventricle and subpulmonary ventricular septal defect (left-sided Taussig-Bing malformation of Lev et al.[11]); and Group II-2, malattachment of the mitral valve leaflet apparatus into the contralateral ventricle—two patients with discordant criss-cross A-V connections (l-bulboventricular loop) and transposition of the great arteries (aorta from the right ventricle[12,13]).

Analysis of cases: Clinical, echocardiographic, electrocardiographic, hemodynamic, angiographic and anatomic data at postmortem examination were available for analysis (Table I). M mode echocardiograms, obtained with an Ekoline echocardiograph connected to an 1856 Honeywell strip chart recorder and a 2.25 or 3.5 megahertz transducer, were available in all patients. Sector scans were obtained in 9 of 10 patients using an 80° phased-array system (Varian Associates V-3000 scanner). Long axis, short axis, apical, subxiphoid and suprasternal views were recorded, and stop frame photographs were obtained from videotape recordings.

Results

The clinical findings and course of the 10 patients are summarized in Table I. Data in these patients were subdivided according to the atrioventricular (AV) valve involved and the type of atrioventricular malposition.

Group I

Group I-1: This subgroup included four patients (Cases 1 to 4) with hypoplastic right ventricle, malposition (straddling) of the tricuspid anulus across a posterior ventricular septal defect (A-V canal type) above the left ventricle, and malattachment of portions of the tricuspid valve to the left ventricular septum or papillary muscles, or both. The electrocardiogram indicated a hypoplastic right ventricle (left ventricular hypertrophy or lack of anterior forces) and a posterior type of ventricular septal defect (left axis deviation with counterclockwise loop in the frontal plane) in three of these four cases. Angiograms were diagnostic of a small right ventricle, ventricular septal defect (location uncertain), transposition of the great arteries (S,D,D) and straddling of the tricuspid anulus across the defect above the left ventricle in all four patients (Fig. 1A).

M mode echocardiograms in all patients revealed a greatly hypertrophied but hypoplastic anterior ventricle. The mitral valve and parts of the tricuspid valve apparatus were located in the left ventricle. During ventricular diastole the anterior (septal) tricuspid leaflet traversed the interrupted septal echo space (ventricular septal defect) into the right ventricle (Fig. 2A). M mode scans from the pulmonary artery to the left ventricle obtained at the lower left parasternal area (fourth to fifth interspace) showed both A-V valves without an intervening septum, suggesting a posteriorly situated ventricular septal defect. Echocardiograms at the mid to lower left ventricular cavity revealed a distinct posterior interventricular septum and a small anterior right ventricular cavity.

The sector scans in this group showed a remarkable similarity of the A-V anatomy. The right ventricle was approximately one-third the size of the left ventricle. A large ventricular septal defect was well visualized in long axis, apical and subxiphoid views. The mitral valve was of normal size with normally mobile leaflets (no stenosis) and was connected to the papillary muscles in the left ventricle. In the long axis view, the tricuspid valve was seen to course from the anterior aspect of the pulmonary artery across the ventricular septal

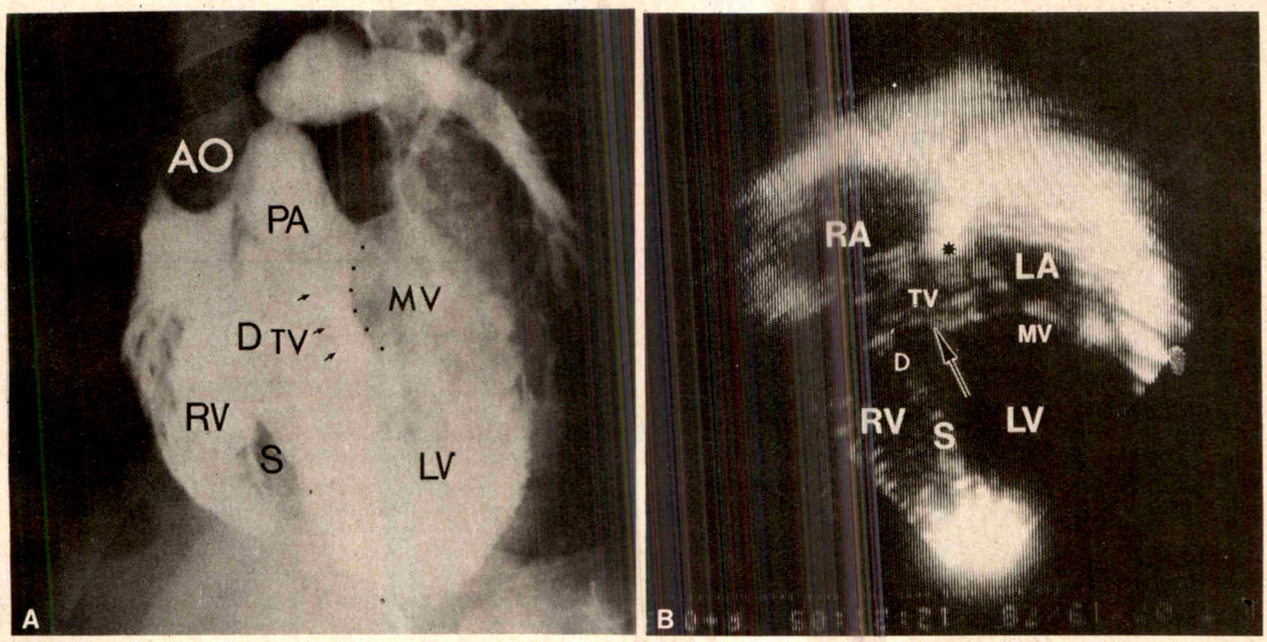

FIGURE 3. Case 2 (Group I-1). **A**, right ventricular angiogram (left anterior oblique view). d-transposition of the great arteries and tight surgical pulmonary artery (PA) banding are apparent. The right ventricle (RV) is moderately hypoplastic and the ventricular septum (S) is malaligned in relation to the tricuspid valve (TV) anulus, which straddles the interventricular septum across a posterior ventricular septal defect (D). **B**, apical view sector scan recorded in a more posterior plane than that of the angiogram. The central fibrous body (**asterisk**) is displaced above the left ventricle (LV) so that almost half of the tricuspid valve anulus straddles the interventricular septum (S). Note the opening of the tricuspid valve (TV) into both the right and the left ventricles.

defect into the left ventricle, where it was confluent with the mitral valve. The right ventricle was small and anterior, and a distinct interventricular septum could be visualized (Fig. 1, B and C). The left ventricular outflow stenosis, when present, was well seen in this view. The apical view was the most informative for the A-V valve; it clearly showed the junction of the A-V anuli (that is, central fibrous body) displaced above the left ventricle. The tricuspid valve opened partly into the left ventricle and partly into the right ventricle (Fig. 3B). In Case 1 it was possible to correlate the postmortem intracardiac anatomy to that recorded on angiograms and echocardiograms (Fig. 1D).

Group I-2: This subgroup included two patients (Cases 5 and 6). Both patients had a normally positioned tricuspid valve anulus and septal malattachment of the portions of the tricuspid valve to the rim of the ventricular septal defect. The right ventricle was larger than normal in Case 5 and slightly hypoplastic in the other. One patient (Case 6) had superoinferior ventricles with a horizontal interventricular septum on angiography (Fig. 4A). The tricuspid valve was in close proximity to the ventricular septal defect, but the actual attachments could not be assessed from the angiogram. The subxiphoid sector scan of this patient (Fig. 4B) confirmed the superoinferior location of the two ventricles. The ventricular septal defect was well visualized and the central fibrous body was not displaced in relation to the crest of the ventricular septum. Malattachment of the septal leaflet of the tricuspid valve to the rim of the ventricular septal defect was seen throughout the cardiac cycle, with prolapse of the leaflet through the defect into the left ventricle during diastole.

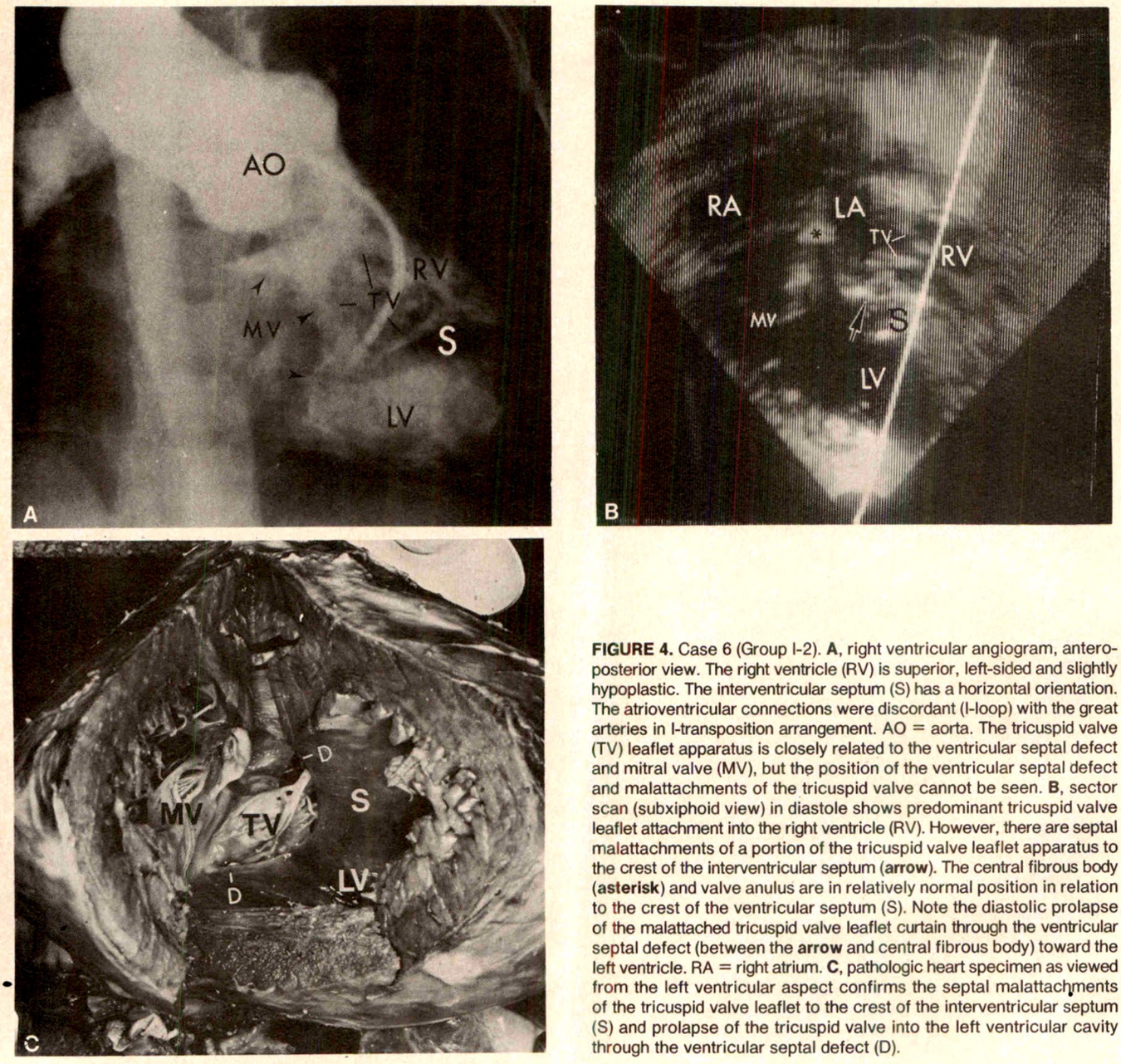

FIGURE 4. Case 6 (Group I-2). **A**, right ventricular angiogram, anteroposterior view. The right ventricle (RV) is superior, left-sided and slightly hypoplastic. The interventricular septum (S) has a horizontal orientation. The atrioventricular connections were discordant (l-loop) with the great arteries in l-transposition arrangement. AO = aorta. The tricuspid valve (TV) leaflet apparatus is closely related to the ventricular septal defect and mitral valve (MV), but the position of the ventricular septal defect and malattachments of the tricuspid valve cannot be seen. **B**, sector scan (subxiphoid view) in diastole shows predominant tricuspid valve leaflet attachment into the right ventricle (RV). However, there are septal malattachments of a portion of the tricuspid valve leaflet apparatus to the crest of the interventricular septum (**arrow**). The central fibrous body (**asterisk**) and valve anulus are in relatively normal position in relation to the crest of the ventricular septum (S). Note the diastolic prolapse of the malattached tricuspid valve leaflet curtain through the ventricular septal defect (between the **arrow** and central fibrous body) toward the left ventricle. RA = right atrium. **C**, pathologic heart specimen as viewed from the left ventricular aspect confirms the septal malattachments of the tricuspid valve leaflet to the crest of the interventricular septum (S) and prolapse of the tricuspid valve into the left ventricular cavity through the ventricular septal defect (D).

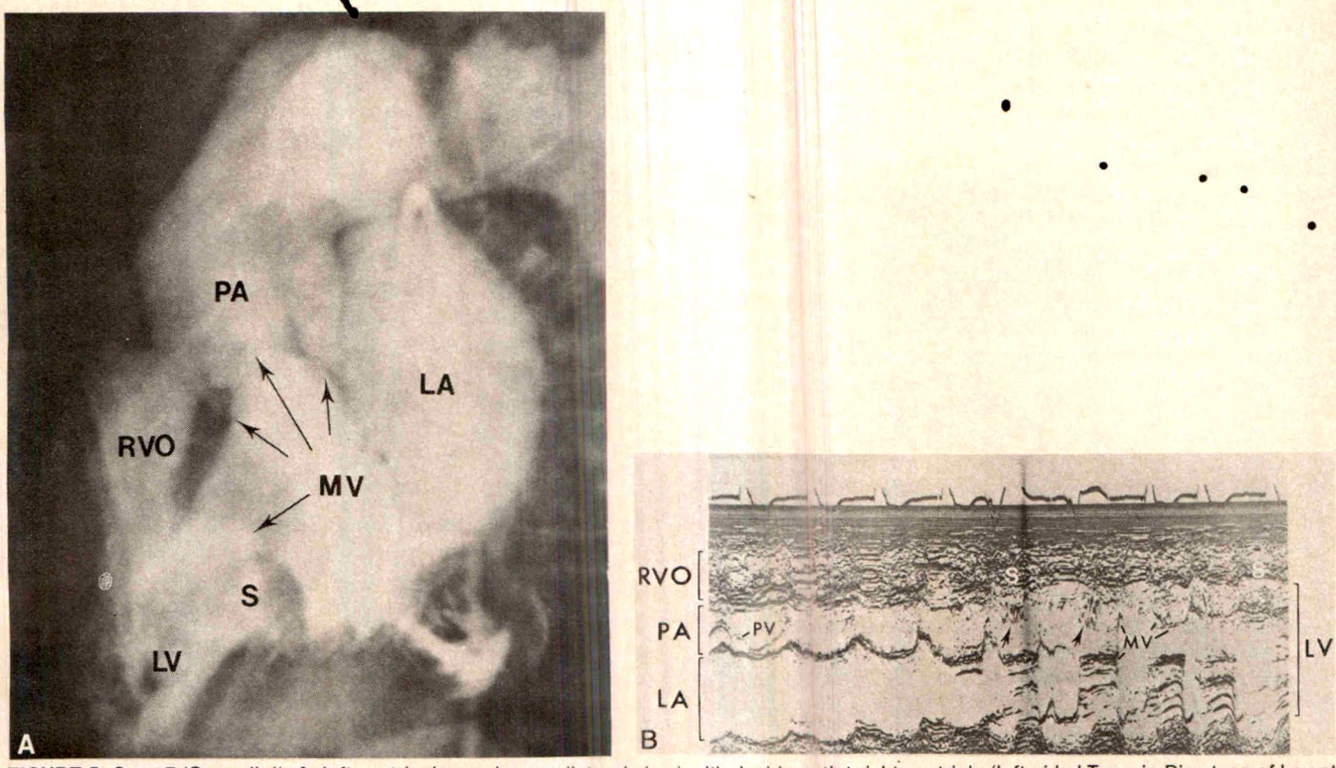

FIGURE 5. Case 7 (Group II-1). **A**, left ventricular angiogram (lateral view) with double outlet right ventricle (left-sided Taussig-Bing type of Lev et al.[11]). The malattachments of the mitral valve (MV) leaflet apparatus to the subpulmonary region (**arrows**) and crest of the ventricular septum (S) are evident and produce subpulmonary outflow right ventricular (RVO) tract stenosis. LA = left atrium; PA = pulmonary artery. **B**, M mode pulmonary artery (PA) to left ventricular (LV) scan reveals abnormal echoes (**arrows**) in the subpulmonary region that are distinct from the anterior leaflet of the mitral valve (MV) and represent abnormal attachments of a portion of the mitral valve in the subpulmonary region. PV = pulmonary valve; RVO = right ventricular outflow tract.

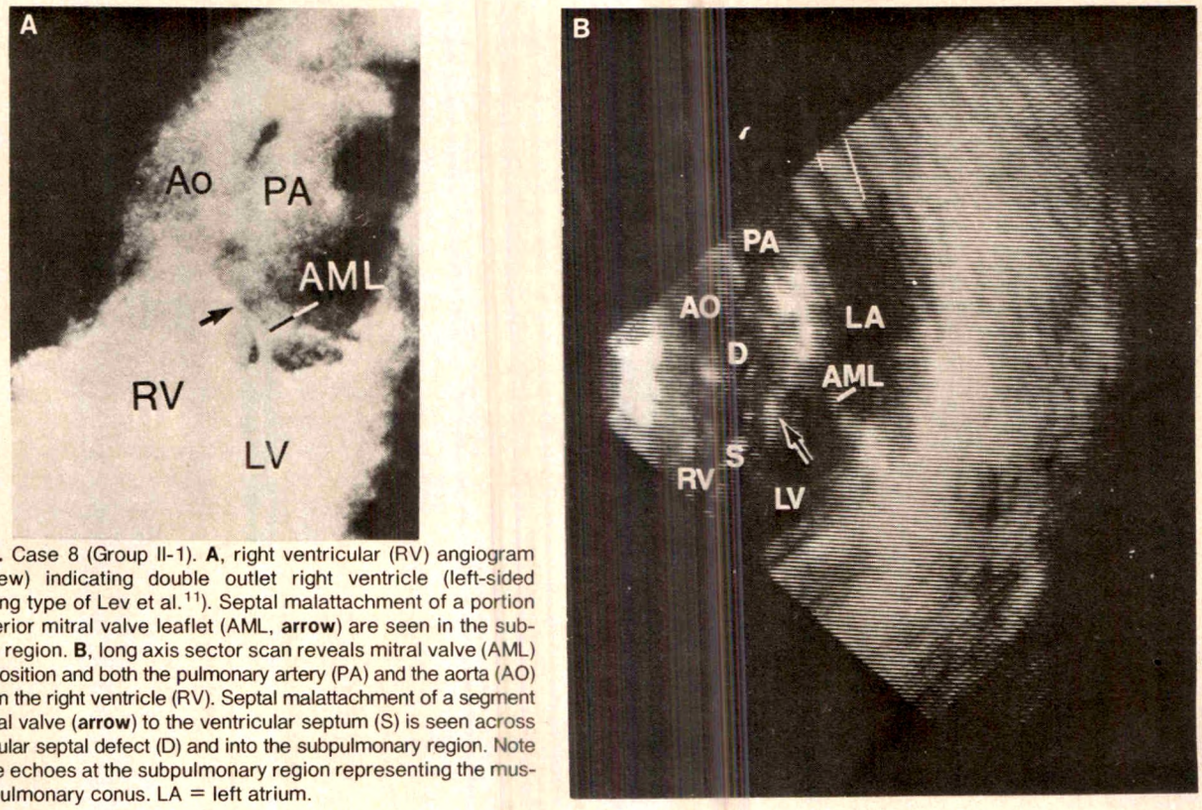

FIGURE 6. Case 8 (Group II-1). **A**, right ventricular (RV) angiogram (lateral view) indicating double outlet right ventricle (left-sided Taussig-Bing type of Lev et al.[11]). Septal malattachment of a portion of the anterior mitral valve leaflet (AML, **arrow**) are seen in the subpulmonary region. **B**, long axis sector scan reveals mitral valve (AML) in closed position and both the pulmonary artery (PA) and the aorta (AO) arising from the right ventricle (RV). Septal malattachment of a segment of the mitral valve (**arrow**) to the ventricular septum (S) is seen across the ventricular septal defect (D) and into the subpulmonary region. Note the intense echoes at the subpulmonary region representing the muscular subpulmonary conus. LA = left atrium.

Group II

Group II-1: This subgroup included two patients (Cases 7 and 8) with a normally positioned mitral valve anulus and mitral valve malattachment, and double outlet right ventricle (left-sided Taussig-Bing malformation of Lev et al.[11]). At postmortem examination, the ventricular septal defect was found to be subpulmonary. A portion of the mitral valve leaflet crossed the ventricular septal defect and was abnormally attached to the right ventricular side of the ventricular septum and additionally into the subpulmonary area. The angiogram of Case 7 showed the anatomy of double outlet right ventricle of the Taussig-Bing type, with the mitral valve tissue bulging into and obstructing the subpulmonary area (Fig. 5A). The anomalously attached mitral valve tissue was not recognized preoperatively. The M mode echocardiogram in this patient (Case 7) revealed abnormal echoes of A-V valve tissue in the subpulmonary region. However, these echoes were erroneously identified as part of the tricuspid valve (Fig. 5B) initially.

The second patient (Case 8) in this group had similar anatomic features on angiography and was diagnosed as having double outlet right ventricle with subpulmonary ventricular septal defect and abnormal obstructing mitral valve attachments to the septum (Fig. 6A). The long axis sector scan echocardiogram (Fig. 6B) demonstrated accessory mitral valve tissue coursing across the subpulmonary region attaching to the rim of the ventricular septal defect and causing subpulmonary stenosis.

Group II-2: This subgroup included two patients (Cases 9 and 10) with so-called criss-cross A-V connections. Both patients had discordant A-V connections with a d-transposed aorta (aorta to the right of the pulmonary artery) arising from the right ventricle. Both patients had a posterior ventricular septal defect with subpulmonary stenosis in one patient and atresia in the other. The angiocardiogram demonstrated that the left atrium was posterior, superior and left-sided and connected anteriorly to the left-sided right ventricular inflow through the tricuspid valve (Fig. 7A). The left ventricle was posterior and adjacent but not connected to the left atrium. Instead, the right atrium communicated with the left ventricle by way of the mitral valve.

The long axis sector scan echocardiogram demonstrated an atretic subpulmonary area, ventricular septal defect and posterior left atrium connected to an anterior right ventricle through the tricuspid valve (Figs. 7, B and C). The right atrium was connected to the posterior left ventricle by way of the mitral valve, which was seen to attach into both the left ventricle (expected attachments) and the right ventricle (abnormal attachments) (Fig. 7 and 8, A and C). The echocardiographic four chamber sector scan showed the abnormal attachments of the mitral valve in the right ventricle, and the anatomic (postmortem) specimen confirmed the criss-cross and straddling relations of the A-V connections. The ventricular-septal axis was abnormal and approximately at right angles to the atrial-septal axis in this view.

Discussion

Anular straddling or overriding versus malattachment of A-V valve: We have used the term malposition of the A-V valves to describe a spectrum of the positional abnormalities of the various components of these valves. These include: (1) anular straddling or overriding of the A-V valve anulus across the ventricular septal defect above the contralateral ventricle with leaflet malattachments, and (2) malattachment of the leaflet apparatus to the interventricular septum or into the contralateral ventricle without anular straddling of the A-V valve. The distinction between anular straddling of the A-V valves with various types of leaflet malattachments and malattachment of the leaflet apparatus without significant anular straddling has important surgical implications. Bharati et al.[14] recently used such distinctions between anular and peripheral straddling for pathologic classification (their peripheral straddling is similar to our definition of malattachment). Tabry et al.[15] discussed the surgical management of straddling A-V valve and stressed the importance of septal (type A and B) and ventricular (type C) malattachments of the leaflet apparatus.

Echocardiographic diagnosis of types of malattachment of A-V valve: Angiography can define ventricular chamber size, A-V relations and the position of the great vessels; however, details of the A-V valve anatomy are frequently not seen. Sector echocardiography permits viewing this region in various planar projections in real time motion through many cardiac cycles. The extent of anular straddling can be determined by observing the displacement of the central fibrous body in relation to the interventricular septum, and the type of leaflet malattachment can be directly observed. Furthermore, intracavitary dimensions of the two ventricles and the relation between the great vessels can be assessed. Sector echocardiography reliably established the type of A-V malposition in each of our patients, whereas the diagnosis was only suggested from the angiographic study.

Tricuspid valve anular straddling: The anular form of tricuspid valve straddling in our study occurred in association with a hypoplastic right ventricle. There was displacement of the interventricular septum and, hence, nonalignment of the septum to the tricuspid valve anulus. Consequently, the tricuspid valve anulus straddled above the left ventricle through a posterior ventricular septal defect. Additionally, portions of tricuspid leaflets were malattached to the papillary muscles in the left ventricle. The hypoplasia of the right ventricle would seem to preclude surgical correction of these hearts by a Mustard[16] or Rastelli[17] procedure, even if the tricuspid valve could be replaced. A modified Fontan[18] correction, in which the right atrium was connected to the pulmonary artery through a conduit with patch closure of the tricuspid valve anulus was recently reported.[15] An alternative form of repair that involved connecting the left ventricle to the aorta with an intraventricular baffle and the right ventricle to the pulmonary artery by way of a conduit, and replacement of tricuspid valve with prosthesis was also described.[15]

Tricuspid valve malattachment: Malattachments of the tricuspid leaflets without anular straddling occurred in association with an adequate-sized right ventricle. During ventricular diastole, the malattached (to the crest of the ventricular septum) leaflet curtain prolapsed through the ventricular septal defect into the left ventricle, giving a misleading impression of anular straddling or ventricular malattachment in the M mode

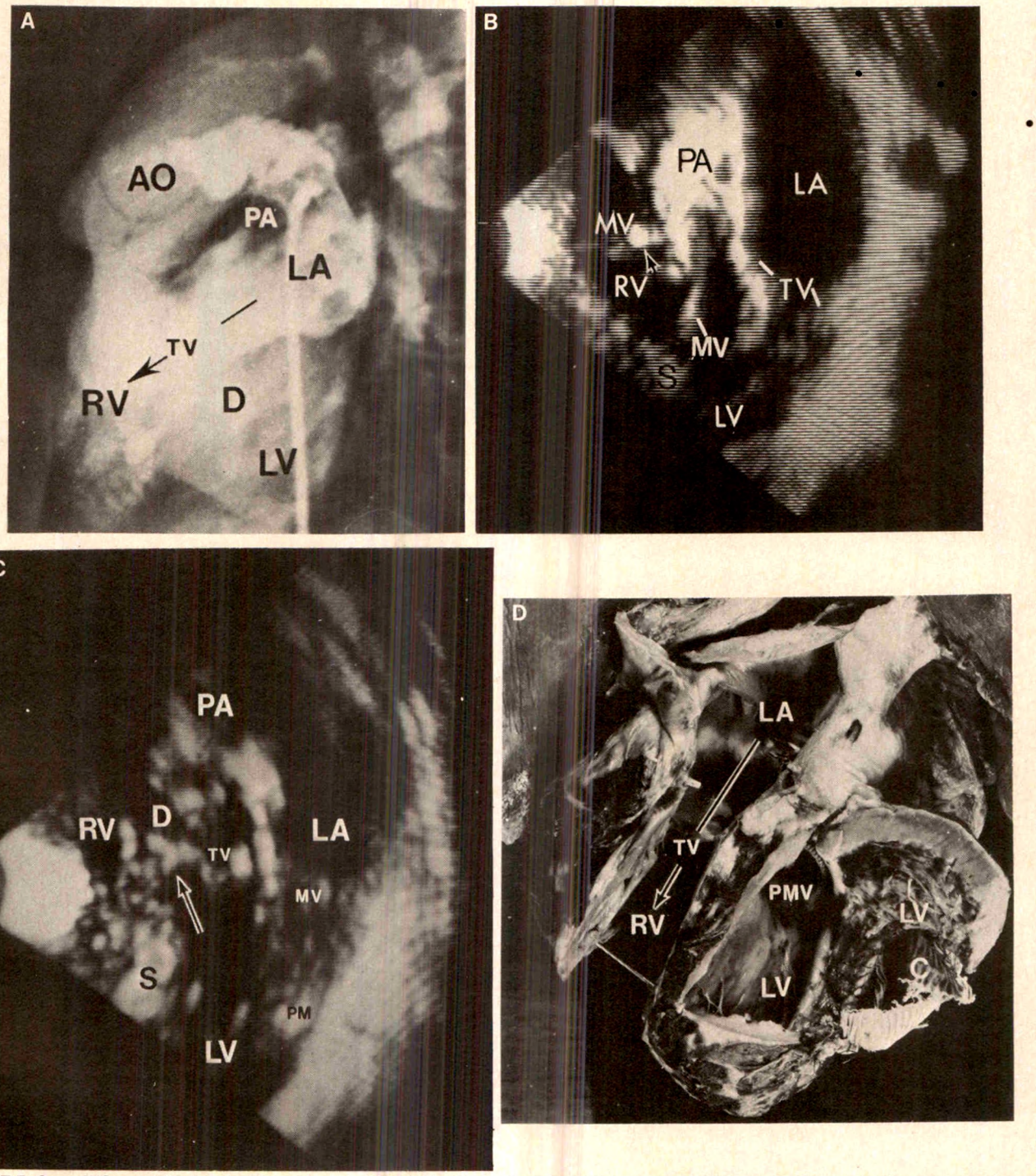

FIGURE 7. Case 9 (Group II-2). **A**, left atrial angiogram (lateral view) indicating discordant criss-cross atrioventricular connections, transposition of the aorta (AO), ventricular septal defect (D) and pulmonary atresia (the pulmonary artery [PA] is opacified by way of the aortopulmonary shunt). The left atrium (LA) is posterior and left-sided, connecting to an anterior right ventricle (RV) by way of the tricuspid valve (TV). The right atrium is connected to the left ventricle posteriorly through the mitral valve. **B and C,** sector scans in the long axis view. **B** shows the tricuspid valve in semiclosed position. Note the apparent concordant relation of the left atrium and left ventricle (LV). During ventricular systole (**B**) the tricuspid valve appears to be connected to the left ventricle; however, during diastole (**C**) it opens into an anterior right ventricle. The apparently concordant tricuspid valve-left ventricular relation is due to the presence of a large ventricular septal defect and criss-cross arrangement of the inflow portions of the two ventricles. The mitral valve shows normal attachments in the left ventricle and ventricular malattachments (**arrow**) in the right ventricle. A large ventricular septal defect extends from the interventricular septum (S) to the base of the pulmonary artery (PA). **D**, pathologic specimen viewed in the same plane as the angiogram confirms the left and right atrioventricular connections. Note the prosthetic valve (PMV) in the mitral valve orifice, replacing the mitral valve apparatus that intraoperatively was malattached into the right ventricle across the ventricular septal defect. C = conduit from the left ventricle to the pulmonary artery.

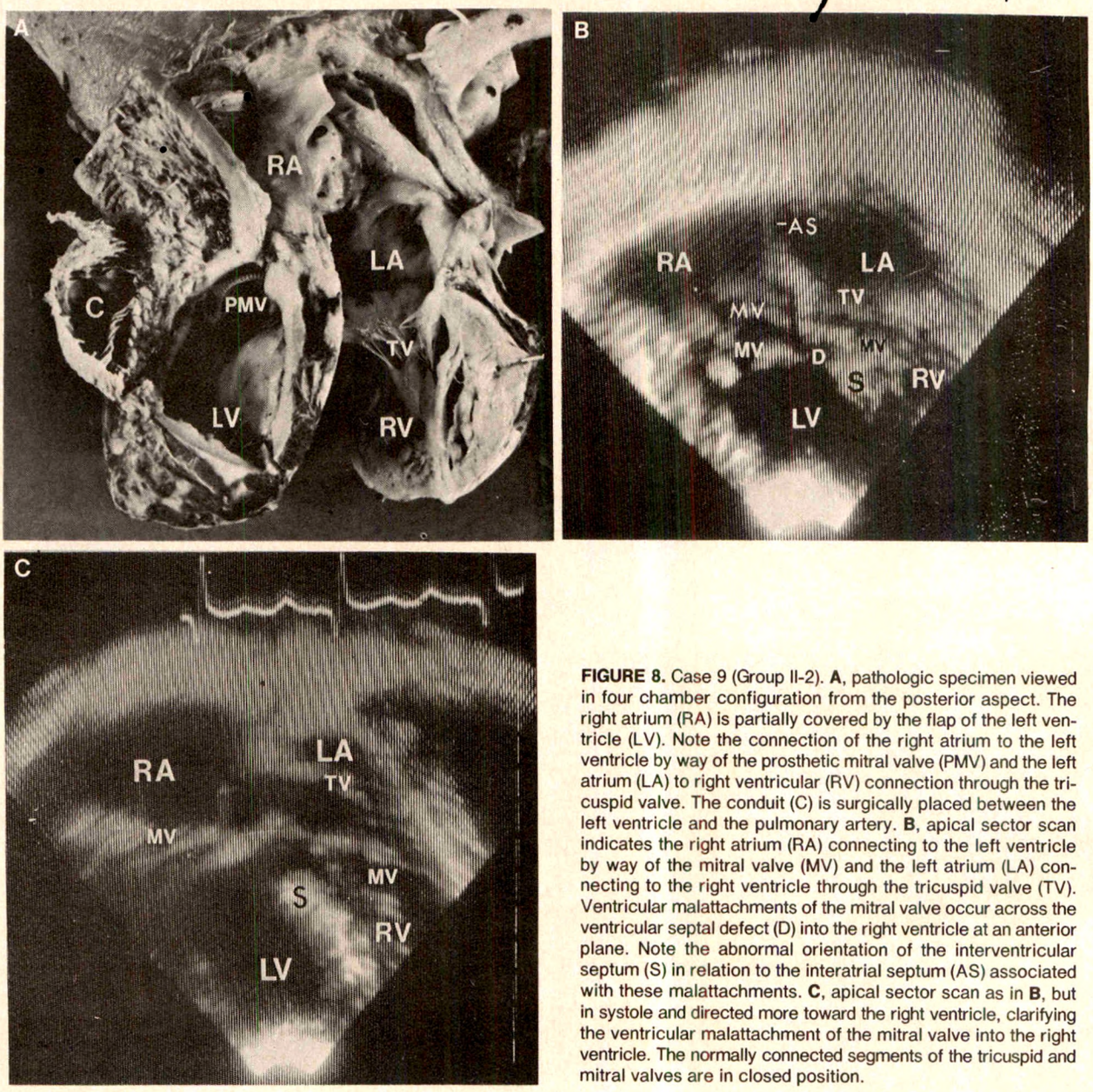

FIGURE 8. Case 9 (Group II-2). **A**, pathologic specimen viewed in four chamber configuration from the posterior aspect. The right atrium (RA) is partially covered by the flap of the left ventricle (LV). Note the connection of the right atrium to the left ventricle by way of the prosthetic mitral valve (PMV) and the left atrium (LA) to right ventricular (RV) connection through the tricuspid valve. The conduit (C) is surgically placed between the left ventricle and the pulmonary artery. **B**, apical sector scan indicates the right atrium (RA) connecting to the left ventricle by way of the mitral valve (MV) and the left atrium (LA) connecting to the right ventricle through the tricuspid valve (TV). Ventricular malattachments of the mitral valve occur across the ventricular septal defect (D) into the right ventricle at an anterior plane. Note the abnormal orientation of the interventricular septum (S) in relation to the interatrial septum (AS) associated with these malattachments. **C**, apical sector scan as in **B**, but in systole and directed more toward the right ventricle, clarifying the ventricular malattachment of the mitral valve into the right ventricle. The normally connected segments of the tricuspid and mitral valves are in closed position.

echocardiogram. Because the interventricular septum was not grossly displaced, anular straddling was not present. Sector scan echocardiography helped identify these partial malattachments to the septum in one patient (Case 6) who underwent a successful intracardiac repair. This study did not encounter a heart in which the tricuspid valve leaflet apparatus was attached to the papillary muscles in the left ventricle without concurrent anular straddling. The reported experience[7] suggests that in such hearts the atrial septum and ventricular septum are malaligned at right angles to each other, permitting the tricuspid valve to be malattached into the contralateral ventricle, through a posteriorly placed ventricular septal defect.

Mitral valve anular straddling: Anular straddling of the mitral valve was not noted in our study, but was reported by Bharati et al.[14] By analogy with tricuspid valve malpositions, anular straddling of the mitral valve can be expected to occur with hypoplastic left ventricle when the ventricular septum is malaligned with the mitral valve anulus.

Mitral valve malattachment: Septal malattachments of the mitral leaflets were observed in our cases of double outlet right ventricle. The mitral valve leaflet apparatus was abnormally attached to the crest of the ventricular septum as well as onto the subpulmonary area. The size of both ventricles was normal or large. Angiographic and echocardiographic findings of the abnormal subpulmonary and septal attachments were confirmed in one of our patients (Case 8) who had successful intracardiac correction. Removal of these abnormal attachments, even when recognized intraoper-

atively, is not considered feasible without complete valve replacement, therefore an alternative approach was used to bypass this area of obstruction with a left ventricle to pulmonary arterial conduit.[19]

Ventricular malattachments of the mitral valve leaflet apparatus were observed in two hearts with discordant (l-loop) and criss-cross A-V connections. In our experience, gross ventricular malpositions, in which inflow portions of the ventricles cross, are usually associated with positional abnormalities of the A-V valves. In these two hearts the atrial and ventricular septa were malaligned and consequently the mitral valve was malattached to the right ventricle, but without significant anular straddling.

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Two-Dimensional Echocardiographic Characteristics of Double Outlet Right Ventricle

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The reliability was evaluated of two dimensional echocardiography in distinguishing double outlet right ventricle from other anomalies of the great arteries. Accordingly, a combined retrospective and prospective study was conducted in 13 children with double outlet right ventricle, 12 with tetralogy of Fallot, 13 with complete d-transposition of the great arteries, 5 with congenitally corrected l-transposition and 2 with truncus arteriosus. Echographic findings using a standard long axis view in all subjects with double outlet right ventricle included (1) inability to identify a great artery arising from the left ventricle, and (2) lack of continuity between the anterior mitral leaflet and any semilunar valve. In the short axis view constant findings were (1) simultaneous imaging of both great arteries in an anterior location with the ventricular septum identified posteriorly on sweeping into the left ventricle, and (2) lack of a clockwise wraparound of the aorta by the right ventricular outflow tract. Imaging revealed that the great arteries were side by side in seven patients, d-malposed in three and l-malposed in two. A modified left precordial tomographic view demonstrated both great arteries arising from the right ventricle in four of nine patients not treated surgically. In four patients with surgically repaired double outlet right ventricle, the left ventricular outflow tract had a tunnel-like configuration in the long axis view. These findings were diagnostic of double outlet right ventricle in all patients and accurately differentiated the malformation from other anomalies of the great arteries.

Double outlet right ventricle is a rare congenital malformation that appears to result from a lack of conotruncal inversion, a failure of leftward conoventricular shift and persistence of a subaortic conus.[1,2] Neufeld et al.[3–5] classified double outlet right ventricle into two categories: one associated with pulmonary stenosis and one without pulmonary stenosis. The ventricular septal defect may be remote from or related closely to one or both semilunar valves. The great arteries may either be side by side, d-malposed, l-malposed or normally related.[6]

The diagnosis of double outlet right ventricle with M mode echocardiography relies principally on demonstration of mitral semilunar valve discontinuity, although the recognition of discontinuity may be difficult technically.[7–10] When our group[11,12] introduced real time, two dimensional echocardiography as an important advance in the evaluation of congenital heart disease, we used a linear array system and provided a brief description of the findings in double outlet right ventricle.[11] Sector scan techniques were employed subsequently to provide higher resolution images of anomalies of the great arteries.[13,14] These earlier two dimensional echocardiographic findings in patients with double outlet right ventricle describe two great arteries appearing anterior to the interventricular septum in the short axis view with the leftward great artery coursing in a posterior direction toward the lungs. The aim of the present

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TABLE I
Patient Group

Anomaly of Great Arteries	Cases (no.)	Palliative Operation or No Surgery	Operative Repair	Associated Malformations
Tetralogy of Fallot	12	6	6 (1 with RV-PA conduit)	None
Complete d-transposition or malposition	14	8	6 (5 Mustard, 1 RV-PA conduit)	VSD (5), PS (3), tricuspid atresia (2), ECD (1), coarctation (1), straddling TV (1), single ventricle (1)
Corrected l-transposition or malposition	5	5	0	VSD (3), Ebstein's anomaly of TV (2), single ventricle (1)
Truncus arteriosus	2	1	1	None
Double outlet right ventricle	13	9	4 (1 RV-PA conduit)	PS (6)
Totals	46	29	17	

ECD = endocardial cushion defect; PA = pulmonary artery; PS = pulmonary stenosis; RV = right ventricle; TV = triscuspid valve; VSD = ventricular septal defect.

study was to define more comprehensively the anatomic spectrum on two dimensional echocardiography and to determine the reliability of this ultrasonic technique in distinguishing double outlet right ventricle from other malformations of the great arteries.

Methods

Echocardiography: Real time, two dimensional echocardiographic studies were performed with a commercially available phased array sector scan instrument (Varian Associates, V-3000). The transducer was composed of 32 piezoelectric crystals, 2.25 megahertz, with an external acoustic lens for focusing the ultrasonic beam. The ultrasonic beam was electronically steered through an arc of 84°. The sector images were projected in real time and recorded on 1 inch (2.54 cm) video tape at 30 frames/sec. All patients were examined in the left lateral decubitus position with multiple transducer positions from the precordium and apex. Views were achieved of the left and right ventricles in tomographic long and short axis with sweeps to the great arteries. Left precordial long axis views with a slight superior medial angulation to visualize the great arteries were also used.

Patients: Forty-six patients with anomalies of the great arteries were examined (Table I). Diagnoses were confirmed with biventricular cineangiography in each patient and also at operation in 17 patients. Thirteen patients had double outlet right ventricle, 12 had tetralogy of Fallot, 14 had complete d-transposition or malposition of the great arteries, 5 patients had congenitally corrected l-transposition or malposition and 2 patients had truncus arteriosus. There were no patients with asplenia, polysplenia or dextrocardia syndromes. Table II more completely describes the patients with double outlet right ventricle who were categorized as having a type I malformation (infracristal or subaortic ventricular septal defect, [eight patients]) or a type II malformation (supracristal or subpulmonary ventricular septal defect [five patients]). The mean age of these 13 patients was 6.5 years (range 2 months to 15 years). The mean age of the other patients studied was 5.5 years (range 5 months to 16 years).

Results

Normal anatomy: The anatomy of the normal left ventricle in standard long axis and short axis two dimensional views has been described.[15] In the long axis

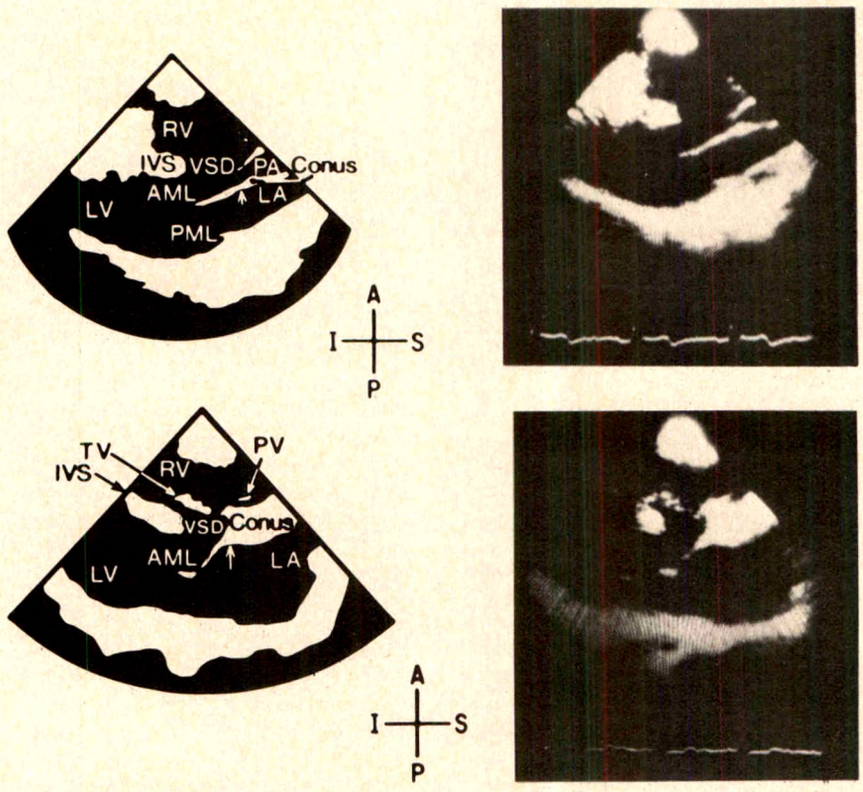
TABLE II
Thirteen Patients With Double Outlet Right Ventricle

Case no.	Age	Type DORV	Orientation of Great Arteries	Surgical Procedure
1	21 mo	I	Side by side	PA banding (1 mo)
2	16 mo	I	Side by side	(Died)
3	8 yr, 6 mo	I	Side by side	PA band (2 mo); complete repair (5 yr)
4	7 yr	I w/PS	d-malposition	Waterston anastomosis (10 d)
5	10 yr, 6 mo	I w/PS	Side by side	Waterston anastomosis (3 yr); complete repair (6 yr)
6	5 yr, 6 mo	I w/PS	Side by side	Waterston anastomosis (4 yr); complete repair (6 mo)
7	10 yr	I w/PS	l-malposition	Complete repair with prosthetic RV-PA conduit (9 yr)
8	15 yr	I w/PS	l-malposition	Blalock-Taussig shunt (5 yr)
9	10 mo	II	Side by side	PA band (1 mo.)
10	9 yr, 8 mo	II	d-malposition	PA, band, Blalock-Hanlon atrial septectomy (4 yr)
11	2 mo	II	d-malposition	PA band (2 mo)
12	8 mo	II	Side by side	No surgery
13	9 yr	II w/PS	l-malposition	No surgery

DORV = double outlet right ventricle; PA = pulmonary arterial; PS = pulmonary stenosis; RV = right ventricle; w/ = with.

view the aorta arises from the left ventricle and the anterior leaflet of the mitral valve hinges at the aortic root in fibrous continuity with the aortic valve. A short axis sweep from the left ventricle to the base of the heart shows the left ventricular outflow tract arising from the posterior ventricle and the right ventricular outflow tract wrapping around the aorta in a clockwise fashion.

Double outlet right ventricle: In the standard long axis view inability to identify any great artery emerging from the left ventricle was a feature in all nine patients with double outlet right ventricle who had not under-



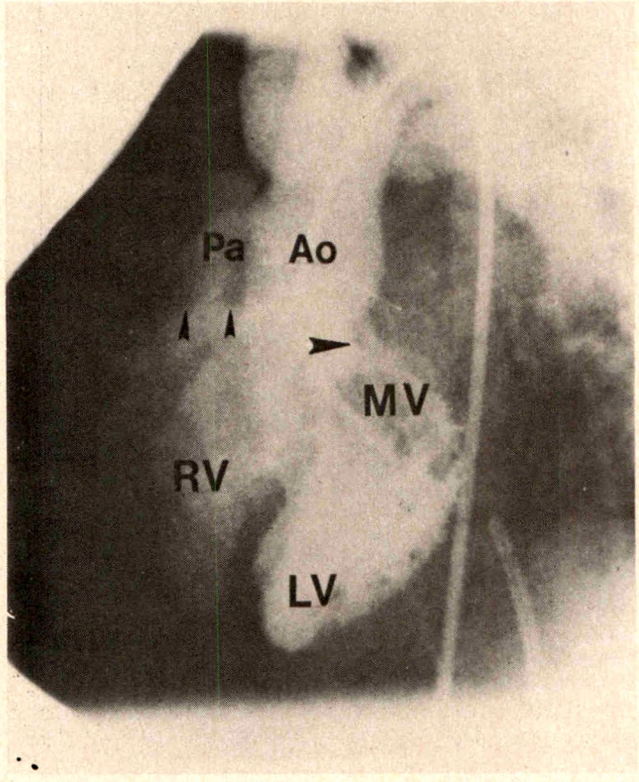


FIGURE 1. Top, Patient 4. Long axis view of the left ventricle in double outlet right ventricle with pulmonary stenosis. The pulmonary artery (PA) is small. The hinge point **(arrow)** of the anterior mitral leaflet (AML) is separated from the pulmonary artery by a conus that appears small, possibly as a result of a hypoplastic pulmonary artery, and less conspicuous than the large conus evident in the **center panel.** There is a large ventricular septal defect (VSD). **Center,** Patient 10. Long axis view of the left ventricle in double outlet right ventricle without pulmonary stenosis. The pulmonary artery is large and separated from the hinge point **(arrow)** of the anterior mitral leaflet by an echo structure (the conus). There is a large ventricular septal defect. No great artery originates from the left ventricle. PV = pulmonary valve; TV = tricuspid valve. **Bottom,** Patient 8. Left ventricular angiogram in the long axis view from a patient with double outlet right ventricle, l-malposition of the aorta (Ao) and pulmonary stenosis. There is discontinuity between the mitral valve (MV) and the semilunar valves produced by the subaortic conus **(horizontal arrow).** The aorta and the pulmonary artery (Pa) emerge from the right ventricle. This angiographic view is the equivalent to the echographic long axis view demonstrated in the other two panels. A = anterior; I = inferior; IVS = interventricular septum; LA = left atrium; LV = left ventricle; P = posterior; PML = posterior mitral leaflet; RV = right ventricle; S = superior. **Vertical arrows** indicate subpulmonary conus.

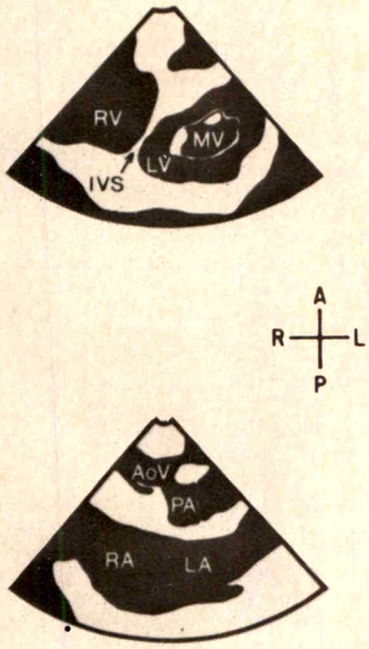
gone corrective operation. The leftward great artery (the pulmonary artery) was usually imaged emerging from the right ventricle, or partially from the right and partially from the left ventricle (Fig. 1, top). In all patients no continuity existed between the anterior leaflet of the mitral valve and the imaged semilunar valve. This lack of continuity could be identified easily as an echo-dense area, representing left-sided conal tissue, between the hinge point of the anterior leaflet of the mitral valve and the posterior margin of the root of the great artery (Fig. 1, center). The two dimensional long axis view was compared with the angiographic long axis view (Fig. 1, bottom). These two long axis characteristics were found in all nine patients who had not undergone operative repair.

In the short axis view the major observation in seven of nine patients was the simultaneous imaging of both great arteries in an anterior location and identification of the ventricular septum posteriorly on sweeping from the left ventricle to the base of the heart (Fig. 2). Another constant short axis finding was the absence of a clockwise rotation of the right ventricular outflow tract around the aorta, which is also seen in all forms of transposition. The relations of the great arteries were abnormal in all of the patients with double outlet right ventricle. Thus, there were four patients with side by side great arteries (Fig. 3, top), three with d-malposition (Fig. 2, bottom) and two with l-malposition (Fig. 3, center). In four of the nine patients left precordial positions of the transducer with a slightly superior, medial angulation was helpful in imaging the origin of both great arteries from the right ventricle (Fig. 4).

Postoperative double outlet right ventricle: Four patients underwent operative repair performed by patching the ventricular septal defect channeling left ventricular outflow into the aorta. Thus, a left ventricular outflow tract tunnel was created by the ventricular septal patch and the subaortic conus (Fig. 5). On sweeping from the left ventricle to the base of the heart in short axis in these patients, both great arteries were still visualized anterior to the ventricular septum. A clockwise wraparound of the aorta by the right ventricular outflow tract was absent. Three patients continued to demonstrate side by side great arteries (Fig. 3, top).

One patient with double outlet right ventricle and pulmonary atresia underwent correction with a conduit containing a porcine heterograft from the right ventricle to the distal pulmonary arteries. In the long axis view, septal aortic continuity was visualized as a thick, dense linear echo producing a tunnel-like configuration of the left ventricular outflow tract. The dense echo of the conus between the anterior leaflet of the mitral valve and the root of the aorta was also imaged. However, in short axis view the conduit appeared to wrap around the aorta in the manner of a normal right ventricular outflow tract. The heterograft valve was imaged within the conduit as an area of multiple dense echoes in a pulmonary valve position (Fig. 3, bottom).

Tetralogy of Fallot: The echocardiographic characteristics noted in tetralogy of Fallot were similar to those we[11] and others[16] have previously noted. In the long axis view normal fibrous continuity was detected between the hinge point of the anterior mitral leaflet and the posterior aortic root. The aortic root was dextroposed and overrode the ventricular septum in all patients who had not undergone surgical repair (Fig. 6). In the short axis view the aorta was seen to arise from



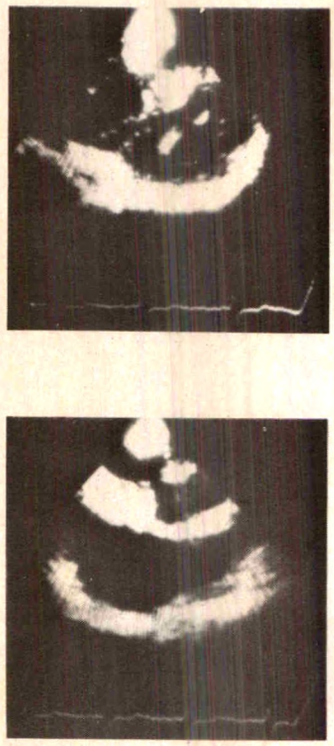


FIGURE 2. Top, Patient 10. Short axis sweep of double outlet right ventricle. level of mitral valve (MV). **Bottom,** level of great arteries. The aorta (Ao) and pulmonary artery (PA) are anterior to the interventricular septum (Ivs). The aorta is anterior and to the right of the pulmonary artery (d-malposed). This is the identical situation that is imaged in complete transposition. This patient had a Blalock-Hanlon septectomy, which may explain the absence of the atrial septum. AoV = aortic valve; L = left; R = right; RA = right atrium; other unidentified abbreviations as in Figure 1.

the posterior ventricle during the sweep from the ventricle to the root of the heart. In four of the six patients short axis imaging of the base of the heart showed a clockwise wraparound of the aorta by the right ventricular outflow tract and the pulmonary valve. In two patients with pulmonary atresia neither the pulmonary valve nor the right ventricular outflow tract was imaged. After surgical repair septal-aortic continuity was seen as a thick, dense linear echo (the septal patch). In contrast to patients with double outlet right ventricle the left ventricular outflow tract appeared normal in the long axis view. In the short axis view, the clockwise rotation of the right ventricular outflow tract around the aorta was imaged in patients with tetralogy of Fallot.

d-transposition of the great arteries: In four patients with uncomplicated, complete d-transposition of the great arteries, both mitral-semilunar valve and septal-great arterial continuity were regularly observed. A sweep from the left ventricle to the base of the heart identified the posterior great artery arising from the left ventricle and the anterior great artery from the right ventricle. The short axis view of the base of the heart showed the aorta directly anterior or anterior and rightward to the pulmonary artery, except in one patient whose aorta was anterior and to the left of the pulmonary artery. As with all forms of transposition, there was no clockwise rotation of the right ventricular outflow tract around the aorta. Postoperative long and short axis findings indistinguishable from those of double outlet right ventricle after repair with a prosthetic conduit were noted in one patient with complete transposition after repair with a right ventricular-pulmonary arterial conduit (Fig. 3, bottom and 5). Six of 10 patients with complete d-transposition had other associated malformations identified echocardiographically, including tricuspid atresia, single ventricle, endocardial cushion defect and straddling tricuspid valve (Table I).

Congenitally corrected l-transposition of the great arteries: In the long axis view in these five patients with congenitally corrected l-transposition continuity could not be established between the left-sided

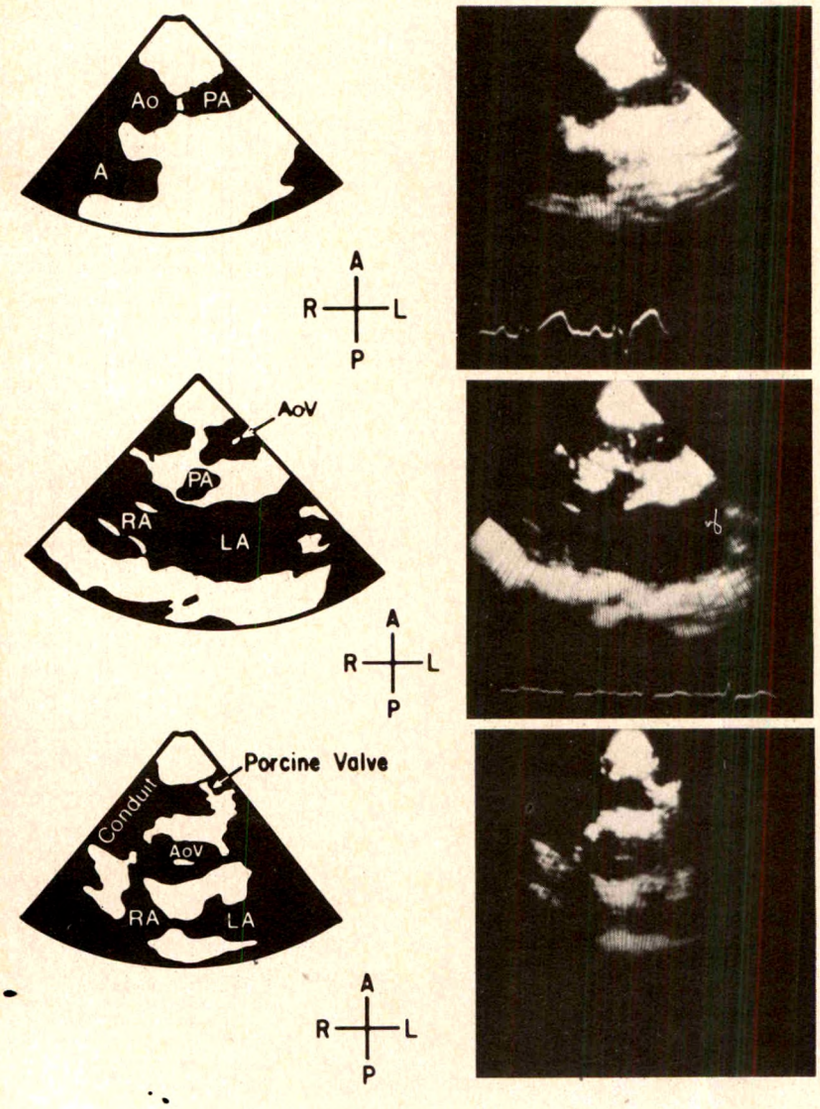


FIGURE 3. Short axis views of double outlet right ventricle. **Top,** Patient 5, with surgically repaired double outlet right ventricle and side by side great arteries. The aorta (Ao) is to the right of the pulmonary artery (PA). In this short axis view, the orientation of the great arteries is identical to that in a few patients with congenitally corrected l-transposition. In the latter anomaly, the pulmonary artery is the rightward great artery. **Center,** Patient 13 with double outlet right ventricle with l-malposition. The aortic valve (AoV) is anterior and to the left of the pulmonary artery (PA). In this short axis view the orientation of the great arteries is identical to that in most patients with congenitally corrected l-transposition. **Bottom,** Patient 7 with double outlet right ventricle surgically corrected with a conduit containing a porcine valve. The conduit wraps around the aorta (Ao) in a clockwise fashion. The porcine valve is seen as an echo-dense area anterior and to the left of the aortic valve. A = (in diagram) atrium; L = left; R. = right; other unidentified abbreviations as in Figure 1.

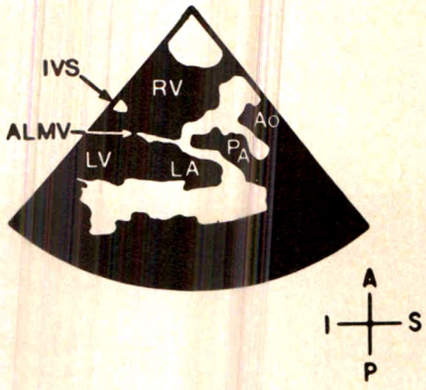
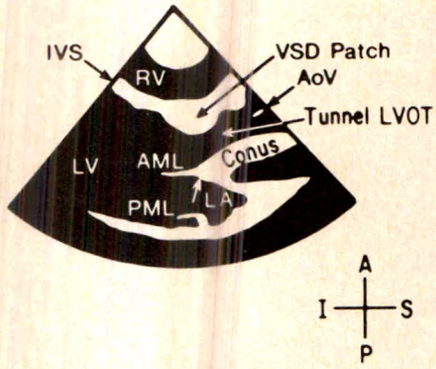


FIGURE 4. Patient 9. Left precordial long axis view with superior angulation to visualize the great arteries. This tomographic view demonstrates the aorta (Ao) to the right of the pulmonary artery (PA) with both arteries arising from the right ventricle (RV). ALMV = anterior leaflet of mitral valve; other unidentified abbreviations as in Figure 1.



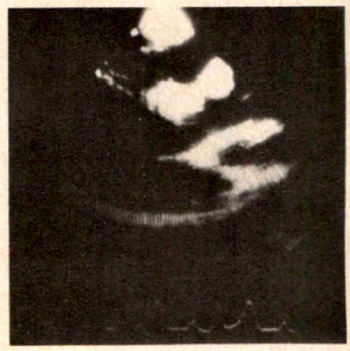
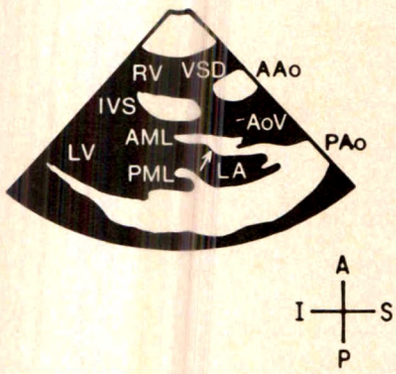


FIGURE 5. Patient 7. Long axis view of the left ventricle in surgically repaired double outlet right ventricle. Continuity is established between the aorta and interventricular septum (IVS) by a thick, dense echo producing a tunnel-like left ventricular outflow tract (LVOT). The hinge point **(arrow)** of the anterior mitral leaflet (AML) is separated from the aortic root by the subaortic conus. AoV = aortic valve; other unidentified abbreviations as in Figure 1.



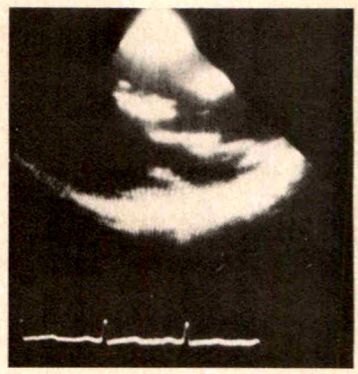


FIGURE 6. Long axis view of the left ventricle in tetralogy of Fallot. The aortic root is dilated and dextroposed causing override of the interventricular septum (IVS). AAo = anterior aorta; AoV = aortic valve; arrow = hinge point of anterior mitral leaflet; other unidentified abbreviations as in Figure 1.

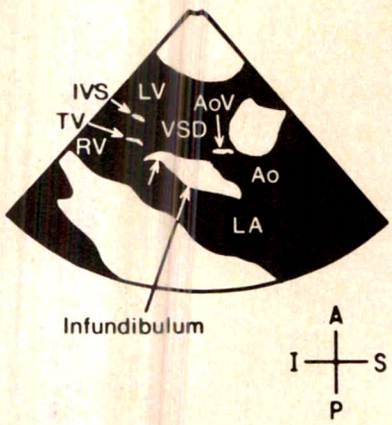


FIGURE 7. Long axis view of the left ventricle (LV) in congenitally corrected l-transposition. The tricuspid valve (TV) is separated from the aortic (Ao) root by an infundibulum. There is a large ventricular septal defect (VSD). The interventricular septum (IVS) is poorly imaged because of its abnormal plane caused by ventricular inversion. AoV = aortic valve; other unidentified abbreviations as in Figure 1.

atrioventricular valve (the tricuspid valve) and the leftward semilunar valve (aortic valve). In these patients an area was observed of increased echo density between the hinge point of the tricuspid valve and the posterior aortic root, probably representing the infundibulum of the right ventricle (Fig. 7). In the short axis view on sweeping from the left ventricle to the base of the heart, the great arteries were seen clearly to arise from separate ventricles. At the base of the heart, either the great arteries were side by side (Fig. 3, top) or the aorta was anterior and to the left of the pulmonary artery (Fig. 3, center). The apical four chamber view with a slight superior angulation also demonstrated the great arteries arising from separate ventricles (Fig. 8). A left-sided Ebstein's anomaly of the tricuspid valve was identified echocardiographically in two patients (a single ventricle in one patient).

Truncus arteriosus: Two patients with truncus arteriosus were studied (Table I). In one patient, not treated surgically override of the ventricular septum by the truncus was difficult to establish, although mitral-aortic continuity was observed clearly. A single great artery appeared to arise from the left ventricle on sweeping from the ventricle to the base of the heart in the short axis. Notably absent was the clockwise wrap-around of the aorta by the right ventricular outflow tract. In the patient with truncus arteriosus with repair by a Rastelli operation, thick dense echoes represented the ventricular septal patch that established continuity between the aorta and the ventricular septum. Mitral-aortic continuity was observed and, at the base of the heart, the porcine valve-containing conduit wrapped around the aorta in a clockwise fashion. These postoperative short axis findings were similar to those seen in the one patient with double outlet right ventricle who had undergone repair with a conduit (Fig. 3, bottom).

Discussion

Echocardiography in differential diagnosis: With or without operative repair, patients with double outlet right ventricle may be distinguished reliably from those with other forms of congenital heart disease by two dimensional sector scanning techniques. Because of the frequent similarity in the clinical presentation of patients with double outlet right ventricle, tetralogy of Fallot and transposition of the great arteries, differential diagnosis is of particular importance. In patients with double outlet right ventricle conal tissue is imaged easily in the long axis view as an area of increased echo density between the hinge point of the anterior mitral leaflet and the root of the leftward great artery. The relative ease of establishing atrioventricular valve-semilunar valve discontinuity with cross-sectional echocardiography substantiates the superiority of this form of tomographic imaging to M mode echocardiography in demonstrating this anatomic phenomenon. A further helpful finding in this view is the absence of any great artery arising from the left ventricle. In the short axis view the essential finding during the sweep from the left ventricle to the base of the heart is that both great arteries arise anterior to the interventricular septum. In this view the absence of a right ventricular outflow tract is helpful but is not diagnostic of double outlet right ventricle because it is also observed in other forms of transposition. The great arteries may be side by side, d-malposed, or l-malposed.[6,17–19]

The identification of double outlet right ventricle with complete transposition of the great arteries is

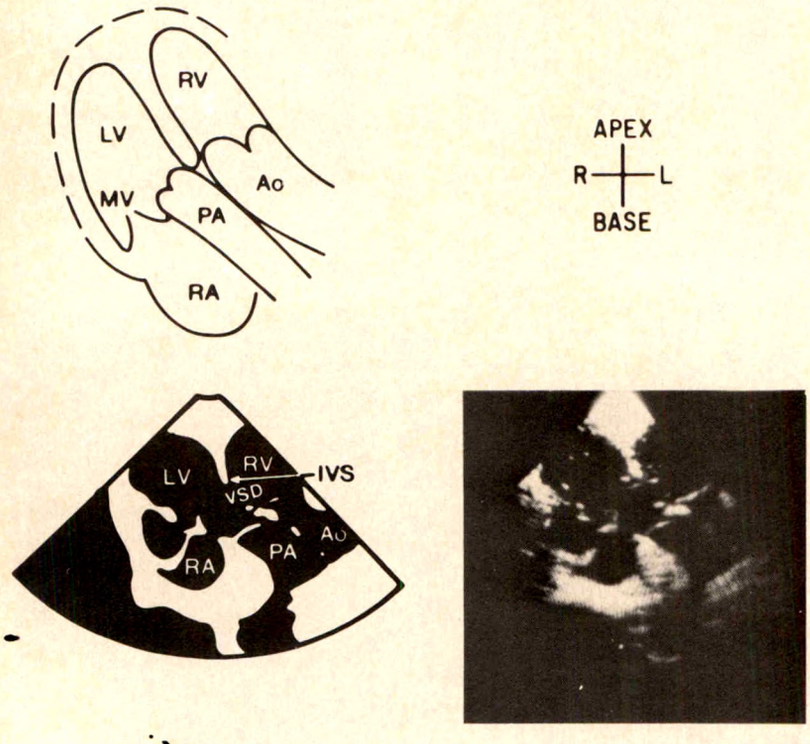


FIGURE 8. Apical view with superior angulation to visualize the great arteries in congenitally corrected l-transposition. Notice the two great arteries arising from separate ventricles and the ventriculoatrial discordance. There is a large ventricular septal defect (VSD). L = left; R = right; RA = right atrium; other unidentified abbreviations as in Figure 1.

facilitated by demonstrating mitral-semilunar (pulmonary) valve continuity in long axis in the latter situation. Six of the patients with double outlet right ventricle had a side by side relation of the great arteries in the short axis view. However, in three patients with double outlet right ventricle and d-malposition findings in the short axis view resembled those in complete d-transposition in which the anterior great artery was also to the right of the posterior great artery. Thus, correct diagnosis of double outlet right ventricle relied on (1) the sweep from the ventricles to the great arteries to establish that both great arteries were anterior to the interventricular septum, and (2) the observation that discontinuity existed between mitral and semilunar valves. The appearance of atrioventricular valve-semilunar valve discontinuity was seen in the standard long axis view in patients with congenitally corrected l-transposition. Thus, distinction was not possible in long axis from patients with double outlet right ventricle in whom the atrioventricular valve-semilunar valve discontinuity is due to the presence of a subaortic conus. The appearance in patients with the former anomaly results because of the presence of a subaortic infundibulum. Moreover, the short axis view with both anomalies may image side by side great arteries or a leftward and anterior great artery. Fortunately, the short axis sweep correctly locates the great arteries anterior to the ventricular septum only in the patients with double outlet right ventricle. The superiorly angulated apical four chamber view was also useful in imaging the relation between the great arteries and the ventricular septum in l-transposition.

Patients with surgically repaired double outlet right ventricle were easily distinguished from postoperative patients with tetralogy of Fallot. Because the aorta is to the right of the pulmonary artery in double outlet right ventricle, the long axis view in these patients shows a tunnel-like left ventricular outflow tract created by the intraventricular conduit; this appearance is absent after repair of tetralogy of Fallot. These two entities are distinguished further by the findings on sweeping in the short axis view from the ventricles to the base of the heart. The two great arteries remain in an anterior location after surgical repair or double outlet right ventricle and are either side by side or malposed. In contrast, the patch across the right ventricular outflow tract usually creates a clockwise wraparound of the aorta by the right ventricular outflow tract in tetralogy of Fallot. When an external conduit is used in the repair of complete d-transposition, double outlet right ventricle, tetralogy of Fallot or truncus arteriosus, the short axis view at the base is similar and does not serve to delineate the underlying pathologic features.

Clinical implications: This ability to distinguish double outlet right ventricle from other anomalies of the great arteries with sector scanning techniques is of significant clinical importance, particularly before hemodynamic and angiographic study. There is a limit to the amount of angiographic contrast material that can be used at cardiac catheterization, especially in infants and young children.[20] Now that a variety of axial angiographic views[21,22] may provide precise anatomic details of complex cardiac malformations, two dimensional cardiac ultrasonic imaging may be expected to play an important role in selecting the most appropriate angiographic cross sections.

Acknowledgment

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M mode versus pulsed Doppler echocardiography: Total anomalous pulmonary venous drainage may be suspected from the M mode echocardiogram alone with findings of right ventricular enlargement, paradoxical septal motion and the presence of an echo-free space behind the left atrium.[1] All 33 of our patients had right ventricular enlargement and an unresolved echo-free space. Four of the five infants with proved anomalous pulmonary venous return had paradoxical septal motion; it was also seen in three patients with atrial septal defect, one with ventricular septal defect and tricuspid regurgitation, and two patients who had heart failure with an atrial septal defect, coarctation of the aorta and patent ductus. Although signs of right ventricular volume overload may suggest that the echo-free space behind the left atrium represents a real structure, these signs are not specific for total anomalous pulmonary venous drainage. It is possible that the M mode echocardiographic findings in our patients, combined with the other clinical information, could be used to separate patients with a strong possibility of total anomalous pulmonary venous drainage from those in whom the anomaly is less likely. However, objective and quick pulsed Doppler echocardiographic resolution of the left atrial line is of considerable benefit in confirming the diagnosis and may save an unnecessary and potentially risky, catheterization. For example, we studied some infants with no intrinsic cardiac disease, but with abnormal lung fields on chest X-ray examination and clinical evidence of cor pulmonale, whose M mode echocardiogram revealed significant right ventricular enlargement and a suggestion of pulmonary hypertension from pulmonary valve motion, who also had a left atrial line. Because the variability in radiographic patterns in lung disease and anomalous pulmonary venous return may cause confusion, resolution of the identity of the left atrial line in these patients is important and can be accomplished with pulsed Doppler echocardiography.

Implications: Pulsed Doppler echocardiography provides specific noninvasive differentiation between a rather common artifact and an important diagnostic finding, and it may provide evidence as to whether return to a left superior vena cava is involved in total anomalous pulmonary venous drainage. Before pulsed Doppler echocardiography, a safe, specific noninvasive differentiation between these possibilities was not available. However, the Doppler examination must be performed with care and may require that the precordial transducer position be lower than normal to determine direction of flow in an anomalous venous channel. Although this technique will allow differentiation between a common artifact and a real anomalous return channel, and therefore may bear directly on the decision for cardiac catheterization, invasive study will still be required for detailed assessment of the sites of anomalous drainage and assessment of the degree of obstruction.

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Pulsed Doppler Echocardiographic Detection of Total Anomalous Pulmonary Venous Return: Resolution of Left Atrial Line

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During precatheterization M mode echocardiographic examination, 33 infants were identified as having findings including right ventricular enlargement and presence of a line within the left atrial portion of the M mode tracing suggesting the possibility of cor triatriatum or total anomalous pulmonary venous return. Pulsed Doppler echocardiography was used to sample blood characteristics on either side of the left atrial line to determine which line was artifactual and which was indicative of an important structure. Five patients whose blood flow characteristics were different on either side of the left atrial line were subsequently proved to have total anomalous pulmonary venous return at cardiac catheterization. In the remaining infants blood flow characteristics were identical on either side of the line, and catheterization excluded total anomalous pulmonary venous return and cor triatriatum. In all patients who had total anomalous pulmonary venous return, drainage involved a persistent left superior vena cava, and this vascular structure was identified by pulsed Doppler examination from the suprasternal notch. Pulsed Doppler echocardiography appears to be a useful technique for resolution of left atrial lines found on M mode echocardiography.

During routine M mode echocardiographic examinations of pediatric patients, it is not uncommon to find a line within the left atrial portion of the tracing. That line may be (1) an artifact, representing a reflection from the mitral valve ring; or (2) nonartifactual and normal, representing a normal pulmonary vein entering the left atrium; or (3) nonartifactual and abnormal, suggesting either cor triatriatum or total anomalous pulmonary venous return, with a common pulmonary vein lying behind the left atrium.[1,2] We have used pulsed Doppler echocardiography to evaluate blood flow characteristics on either side of such left atrial lines, to determine which line is artifactual and which is indicative of an important structure.

Pulsed Doppler echocardiography provides noninvasive information concerning blood flow characteristics at known locations within the heart and great vessels.[3] In brief, the hand-held transducer emits pulses of ultrasound and compares the emitted frequency with the frequency of back-scattered pulses, at an operator-controlled depth. By comparing the frequencies (detection of Doppler shift), the direction of blood flow with respect to transducer position can be determined. In addition, the unit evaluates the uniformity of the frequency shift over a 1.5 by 3 mm

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operator-controlled position, termed the sample volume. If the frequencies have uniformly been shifted throughout the area of the sample volume, a smooth audio output is produced through the pulsed Doppler unit, and the time interval histographic flow record reflects this uniform shift by a smooth wave formed by the individual dots. In contrast, if disturbed blood flow is present at the position of the sample volume, the multiple directions and velocities of the red blood cells will cause a nonuniform shift of frequencies. This produces a rough audio output through the pulsed Doppler echocardiographic unit, and scattering of the individual dots constituting the time histographic flow record. In this way the technique can provide noninvasive determination of the direction and character of blood flow at known sites within the heart and great vessels.[3,4]

TABLE I

Pulsed Doppler Echocardiographic Flow Characteristics on Either Side of Left Atrial Line in 33 Infants

Case no.	Age (weeks)	Flow Similar on Both Sides	Flow Not Similar*	Diagnosis at Catheterization
1	32	. . .	Yes	TAPVR-LSVC
2	16	. . .	Yes	TAPVR-LSVC
3	12	. . .	Yes	TAPVR, L → LSVC, R → CS
4	16	. . .	Yes	TAPVR-LSVC
5	4	. . .	Yes	TAPVR-LSVC
6	16	Yes	. . .	ASD
7	3	Yes	. . .	CoA, ASD
8	0.4	Yes	. . .	VSD, ASD
9	1.5	Yes	. . .	Trunc Art
10	36	Yes	. . .	TGA, PS
11	9	Yes	. . .	VSD
12	0.6	Yes	. . .	PDA, CoA, ASD
13	8	Yes	. . .	VSD, PDA
14	3	Yes	. . .	CoA, PDA
15	6	Yes	. . .	VSD
16	10	Yes	. . .	AS, CHF
17	11	Yes	. . .	ASD, VSD, MR
18	3	Yes	. . .	VSD, ASD, AS, CoA
19	20	Yes	. . .	Trunc Art
20	7	Yes	. . .	VSD, PDA, TR
21	14	Yes	. . .	PDA, MR
22	12	Yes	. . .	Per Eff
23	0.2	Yes	. . .	TGA, VSD, Pulm Atr
24	8	Yes	. . .	PDA, CLD
25	16	Yes	. . .	PDA, ASD
26	0.3	Yes	. . .	TGA, PDA
27	16	Yes	. . .	ASD
28	12	Yes	. . .	ASD
29	0.4	Yes	. . .	VSD, TR
30	16	Yes	. . .	VSD, Pulm Atr
31	8	Yes	. . .	VSD
32	3	Yes	. . .	DORV
33	3	Yes	. . .	CoA

* Disturbed flow posterior, phasic atrial flow anterior.

AS = aortic stenosis; ASD = atrial septal defect; CHF = congestive heart failure; CLD = chronic lung disease; CoA = coarctation of aorta; CS = coronary sinus; DORV = double outlet right ventricle; L = left; MR = mitral regurgitation; Pulm Atr = pulmonary atresia; PDA = patent ductus arteriosus; Per Eff = pericardial effusion; PS = pulmonary stenosis; R = right; TAPVR-LSVC = total anomalous pulmonary venous drainage to left superior vena cava; TGA = transposition of the great arteries; TR = tricuspid regurgitation; Trunc Art = truncus arteriosus; VSD = ventricular septal defect.

Methods

Patients: During routine precatheterization M mode echocardiographic examinations, a line was noted within the expected left atrial position of the M mode tracing in 33 infants (Fig. 1). These infants (Table I) were under age 9 months; the diagnosis on cardiac catheterization was total anomalous pulmonary venous return in 5 infants, ventricular septal defect in 15, transposition of the great arteries in 4, coarctation of the aorta in 5, truncus arteriosus in 2 and aortic stenosis in 2, with some patients having multiple defects.

Echocardiography: Complete M mode and pulsed Doppler echocardiograms (Advanced Technology Laboratories Models 400A and 600A, 5 megahertz) were obtained before catheterization. For recording of the time interval histographic output, as it appears in the spectral flow records, the pulsed Doppler echocardiographic unit was set up according to the manufacturer's recommendation, with use of a signal amplitude indicator. The threshold control was set at the point where its amplitude trace jumped from baseline. If Doppler gain was too high, the baseline broadened and the histographic signal was altered; if Doppler gain was too low, there was no histographic flow signal. These adjustments were routinely made as sampling sites and gain adjustments changed. Because the signal amplitude indicator appears as an additional channel below the histogram, it was masked during histographic recording to improve clarity of the presentation of the time interval histographic flow records. Cardiac dimensions from the M mode echocardiogram were measured as described in standard references.[5,6] All patients had right ventricular dimensions exceeding top normal values for weight or surface area.

As the left atrial line was detected from a standard precordial approach, pulsed Doppler evaluation of blood flow characteristics was made by positioning the sample volume on either side of the line. If the audio signal and spectral flow record were different, with sample volume on either side of the line, the line was considered to represent a real structure, separating two distinct flow patterns (Fig. 2). In these cases, the pulsed Doppler transducer was angled in an attempt to further determine the direction of flow, and xiphoid and suprasternal approach examinations were performed to search for anomalous venous channels. From the suprasternal notch examination, a large venous channel on the patient's left, with flow toward the transducer, was considered to be a left superior vena cava, with anomalous pulmonary venous return within it (Fig. 3). If flow characteristics on either side of the line were indistinguishable, the line was considered an artifact (Fig. 4). The pulsed Doppler echocardiographic results were compared with subsequent invasive diagnoses. The sonographer was unaware of the working diagnosis at the time of the pulsed Doppler examination.

Results

Twenty-eight of the 33 infants (Table I) had no perceptible difference in blood flow characteristics on either side of the line; in these patients, cardiac catheterization excluded total anomalous pulmonary venous return or cor triatriatum . In five patients, a distinct difference was noted in flow characteristics, with the sample volume on either side of the line. In these five, nonphasic disturbed flow was noted posterior to the left atrial line, and there was very little variation in flow with changes of cardiac cycle. Flow anterior to the line was smooth and had phasic flow characteristics similar to those of the normal left atrial flow pattern. When the precordial transducer was angled, the flow in each pa-

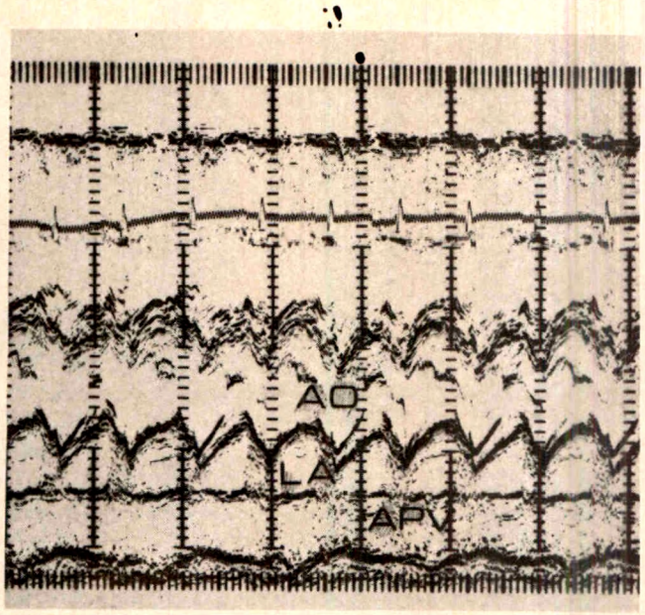

FIGURE 1. M mode echocardiogram, precordial approach. Posterior to the aortic (AO) root, in the position expected for the left atrium (LA), a solid line is seen dividing the left atrium from the anomalous pulmonary vein (APV).

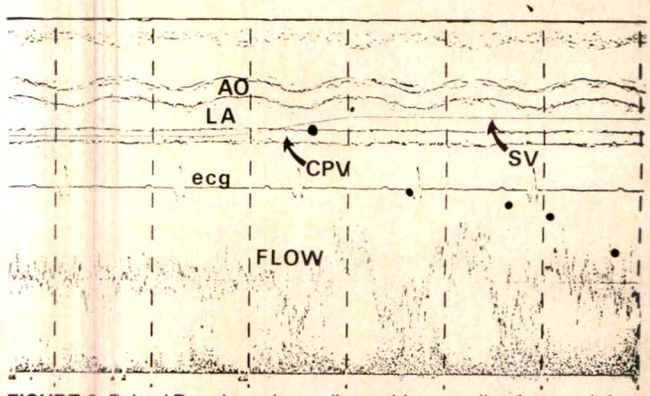

FIGURE 2. Pulsed Doppler echocardiographic recording from an infant with proved total anomalous pulmonary venous return, low precordial approach. At the top of this and all subsequent records is a compressed M mode echocardiogram showing the aorta (AO), left atrium (LA), common pulmonary vein (CPV), and position of sample volume (SV). Below the electrocardiogram (ecg) is the spectral flow record. Flow signals above the line (FLOW) represent flow toward the transducer, and signals below the line, flow away from the transducer. On the left, with sample volume in the common pulmonary vein, flow is slightly toward the transducer and is accompanied by a rough audio signal although the dots are not severely scattered. In the middle, the sample volume (SV) has been moved to the left atrium, and phasic atrial flow is present, greatly differing from the flow pattern obtained in the common pulmonary vein. The signal amplitude indicator channel appears at the bottom, indicating proper gain setting.

tient seemed to be toward the patient's left, and from a suprasternal notch examination a similar turbulent flow pattern was noted, directed toward the suprasternal notch transducer, suggestive of ascending flow in the left superior vena cava. At cardiac catheterization these five patients were confirmed to have anomalous pulmonary venous return to a left superior vena cava. In four patients the anomaly was total, and in the remaining infant, the left lung drained into the left superior vena cava, whereas the right pulmonary venous drainage was into a medially placed coronary sinus.

Discussion

In this series, pulsed Doppler echocardiography was successful in separating those patients whose left atrial line represented a real structure from those in whom it was artifactual. Pulsed Doppler echocardiography was also helpful in identifying supracardiac anomalous pulmonary venous return channels. Because turbulent venous flow ascending on the patient's left toward the suprasternal notch transducer was present in all five infants, a diagnosis of total anomalous pulmonary venous return to the left superior vena cava was made. In four of the five infants, the diagnosis was correct, but in one infant only the left lung drained to that anomalous channel.

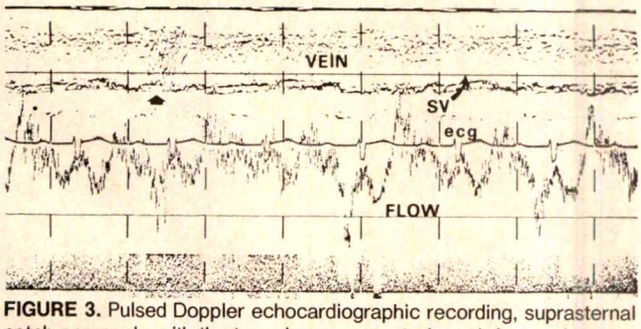

FIGURE 3. Pulsed Doppler echocardiographic recording, suprasternal notch approach, with the transducer encountering a left superior vena cava with ascending flow. After a routine suprasternal notch examination of the aorta and right pulmonary artery, the transducer was angled through the patient's left side, and a large venous structure (VEIN) was encountered. The majority of flow is above the line, toward the suprasternal notch transducer. A 1 cc saline flush with a catheter in the common pulmonary vein deposits contrast echoes in the venous structure (**arrowhead**). SV = sample volume.

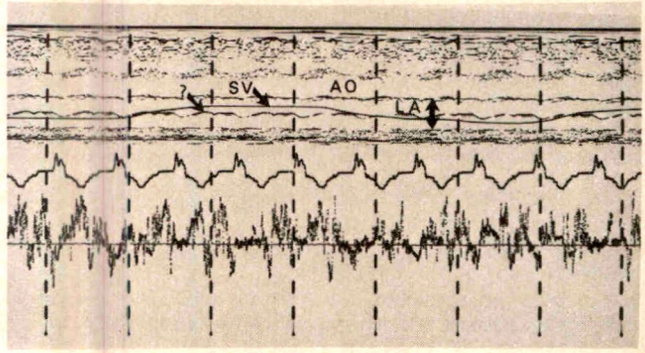

FIGURE 4. Pulsed Doppler echocardiographic record from an infant with a left atrial line, proved right to left atrial shunt, but no anatomic left atrial abnormality. The electrocardiogram is below the M mode record. On the left, the sample volume (SV) is posterior to the left atrial (LA) line, and is rather phasic with some dots scattered, but flow does not differ from flow obtained with the sample volume anterior to the line. Because flows on either side of the line are similar and phasic, the left atrial line (**question mark**) is considered to be an artifact.

In the latter case, pulsed Doppler echocardiography was useful in identifying anomalous pulmonary venous return and a left superior vena cava, but we were incorrect in our interpretation that the flow behind the left atrium actually went into the left superior vena cava. This is an understandable error because the maximal directional information from pulsed Doppler echocardiography is obtained when the angle between the transducer and the moving column of blood is small. When the angle is large (being nearly 90° between precordial transducer and a transversely oriented anomalous pulmonary vein) one may obtain little directional information as to net motion of the column of blood; however, the differentiation between smooth and rough flow at large angles is still possible in most cases. Our error occurred when we angled the transducer in an attempt to follow an expected course of flow, and then encountered the ascending flow in the left superior vena cava and presumed that the two channels were identical. After the correct diagnosis of a mixed type of total anomalous pulmonary venous return was noted, we used a low precordial and xiphoid approach that gave more information concerning the direction of flow in the anomalous vein. This observation suggests that the lower approaches might have been useful in reaching the specific diagnosis before cardiac catheterization. Because in total anomalous pulmonary venous return, the common pulmonary vein is frequently related to the posterior and superior aspects of the left atrium, such a lower than usual approach may be helpful in M mode examinations as well.

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Implications: Pulsed Doppler echocardiography provides specific noninvasive differentiation between a rather common artifact and an important diagnostic finding, and it may provide evidence as to whether return to a left superior vena cava is involved in total anomalous pulmonary venous drainage. Before pulsed Doppler echocardiography, a safe, specific noninvasive differentiation between these possibilities was not available. However, the Doppler examination must be performed with care and may require that the precordial transducer position be lower than normal to determine direction of flow in an anomalous venous channel. Although this technique will allow differentiation between a common artifact and a real anomalous return channel, and therefore may bear directly on the decision for cardiac catheterization, invasive study will still be required for detailed assessment of the sites of anomalous drainage and assessment of the degree of obstruction.

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Increased Systemic Vascular Resistance in Neonates With Pulmonary Hypertension

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The time necessary for aortic diastolic pressure to decrease to 50 percent of an initially selected value after dissipation of the dicrotic notch (T 1/2) was determined in newborn infants with and without pulmonary hypertension. The mean T 1/2 was 671 ± 167 msec in seven infants with clinical evidence of pulmonary hypertension and documented right to left ductus arteriosus shunting; 849 ± 243 msec in nine infants with clinical evidence of pulmonary hypertension but no documented right to left ductus arteriosus shunting; and 457 ± 66 msec in eight infants with hyaline membrane disease and no clinical evidence of pulmonary hypertension or a patent ductus arteriosus. The mean T 1/2 values in the former two groups were significantly different from that in the group with no pulmonary hypertension ($P < 0.01$). An evaluation of factors affecting T 1/2 leads to the conclusion that the patients with pulmonary hypertension had increased systemic vascular resistance as well. This finding has important diagnostic, etiologic and therapeutic implications.

Pulmonary hypertension may cause right to left shunting of blood through the foramen ovale and ductus arteriosus, leading to hypoxemia in certain neonates.[1–8] Some infants with this condition have abnormally increased left ventricular systolic time intervals, which may be due in part to elevated systemic vascular resistance.[8]

Analysis of aortic diastolic pressure can be used to assess systemic vascular resistance.[9] In our study it was used to compare vascular resistance in neonates with and without pulmonary hypertension. Diastolic pressure analysis indicated that the infants with pulmonary hypertension also had increased systemic vascular resistance.

Methods

Patients: Twenty-four infants with no evidence of congenital heart disease were studied with aortic diastolic pressure analysis between December 1975 and January 1977. They were separated into three groups as follows.

Group I (*Table I, A*) included seven infants with pulmonary hypertension causing right to left ductus arteriosus shunting and documented by a right radial to aortic arterial oxygen tension (PO_2) gradient greater than 10 torr in the presence of normal aortic blood pressure (mean aortic pressure = 64/40 mm Hg). Physical findings in this group compatible with pulmonary hypertension included a loud, often single, second heart sound or a systolic murmur heard loudest over the lower left sternal border and sometimes radiating to the right, or both. Additional features to support the diagnosis of pulmonary hypertension included abnormal right preejection period to right ventricular ejection time ratios (RPEP/RVET) determined echocardiographically[8,10] in four infants, hypoxemia refractory to mechanical ventilation[4] in five infants and hypoxemia responsive to tolazoline[4] in two infants. The mean birth weight of these patients was 2,718 g (range 1,480 to 3,657 g). The mean age at the time of their initial study was 2.0 days (range 0.25 to 5 days). The primary radiographic diagnoses were meconium aspiration in three infants, wet lung syndrome in two and hyaline membrane disease in two.

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Group II (*Table I, B*) included nine infants with pulmonary hypertension and no evidence of large volume right to left ductus arteriosus shunting on the basis of the pre- to post-ductus arterial PO_2 gradients. The diagnosis of pulmonary hypertension was supported by physical findings compatible with pulmonary hypertension, abnormal systolic time intervals determined echocardiographically in four infants, hypoxemia refractory to mechanical ventilation in five infants and hypoxemia responsive to tolazoline in four infants. The mean aortic blood pressure in these patients was 65/42 mm Hg when studied, and the mean birth weight was 2,375 g (range 1,219 to 3,374 g). The initial studies were performed at a mean age of 1.3 days (range 0.25 to 3 days). The primary radiographic diagnoses were wet lung syndrome in three infants, hyaline membrane disease in two infants, pneumonia in two infants, meconium aspiration in one infant and no abnormalities in one infant.

Group III (*Table I, C*) included eight infants with no clinical or laboratory evidence of pulmonary hypertension or ductus arteriosus shunting or both. This group of patients constituted part of a larger group previously shown to have no ductus arteriosus shunting.[11] The mean birth weight was 1,579 g (range 794 to 2,438 g). The mean age at the time of the initial diastolic pressure analyses was 1.8 days (range 0.25 to 5 days). The primary radiographic diagnosis was hyaline membrane disease in all eight patients.

Methods: For diastolic pressure analysis, calibrated arterial blood pressure tracings were recorded from abdominal aortic catheters previously placed for blood gas monitoring. The catheter tips were all positioned at the level of the third to fourth lumbar vertebral bodies. The catheters were connected to Hewlett-Packard pressure transducers, and the amplified signal was recorded on a strip recorder at a chart speed of 50 mm/sec. The frequency response of our pressure measurement system was linear up to 20 cycles/sec with a damping coefficient of 0.69, which was adequate to identify the essential physiologic information.[12] The technique used for diastolic pressure analysis was previously described.[11] Briefly, using a semilogarithmic plot of the pressure, we determined the time necessary for the aortic diastolic pressure to decrease to one half the initial value selected 50 msec after dissipation of the dicrotic notch (the half-life or T 1/2).

Data analysis: Duncan's multirange test was used for group comparison because the means of multiple ranges were being compared.[13] The data were converted to logarithms to satisfy the assumption of equal variances in each group. The geometric means were then compared. A probability P value of less than 0.01 was considered statistically significant.

Results (Table I)

Patients with clinical evidence of pulmonary hypertension and documented right to left ductus arteriosus

TABLE I

Clinical Characteristics and Half-Life Data

Patient no.	Birth Weight (g)	Gestational Age (wk)	Postnatal Age (days)	Radiologic Diagnosis	Abnormal RPEP/RVET	Aortic Pressure (mm Hg)	T 1/2 (msec)
A. Patients With Pulmonary Hypertension and Right to Left Ductus Arteriosus Shunting (Group I)							
1	3,200	40	2	MA	+	72/45	950
2	2,722	36.5	5	MA	ND	90/50	488
3	3,178	40	1	Wet lung syndrome	+	72/51	819
4	2,550	36	2	HMD	−	48/30	501
5	2,240	36	2	Wet lung syndrome	+	60/36	692
6	1,480	32	0.25	HMD	ND	42/26	650
7	3,657	40	2	MA	+	67/44	600
Mean	2,718	37.2	2 (range:			64/40	671
SD	721	3.0	0.25–5)				167
B. Patients With Pulmonary Hypertension and No Documented Ductus Arteriosus Shunting (Group II)							
8	1,588	34	2	HMD	−	60/42	620
9	3,374	40	1	MA	+	72/55	870
10	1,219	31	0.25	Pneumonia (Listeria)	ND	72/42	1,175
11	2,070	34	2	Pneumonia (Group B strep)	+	38/21	708
12	3,374	40	0.25	Normal	+	79/47	1,150
13	3,026	40	0.25	Wet lung syndrome	−	79/52	1,120
14	2,381	34	1	Wet lung syndrome	ND	57/37	620
15	2,495	35.5	3	Wet lung syndrome	ND	61/39	575
16	1,850	35	2	HMD	+	68/41	800
Mean	2,375	35.9	1.3 (range:			65/42	849
SD	771	3.3	0.25–3)				243
C. Patients With No Pulmonary Hypertension and No Ductus Arteriosus Shunting (Group III)							
17	840	28.5	0.25	HMD			475
18	1,240	31	5	HMD			526
19	890	28	1	HMD			400
20	794	26	1	HMD			450
21	2,210	34	3	HMD			567
22	2,100	34.5	0.25	HMD			396
23	2,438	36.5	1	HMD			379
24	2,120	35.5	3	HMD			466
Mean	1,579	31.8	1.8 (range:				457
SD	702	3.9	0.25–5)				66

HMD = hyaline membrane disease; MA = meconium aspiration; ND = not done; RPEP = right preejection period; RVET = right ventricular ejection time; SD = standard deviation; T 1/2 = half-life; + = present; − = absent.

shunting (Group I) had a mean T 1/2 of 671 ± 167 msec (standard deviation) (geometric mean [GM] = 654 msec). Infants with clinical evidence of pulmonary hypertension but no documented right to left ductus arteriosus shunting (Group II) had a mean T 1/2 of 849 ± 243 msec (GM = 818 msec). Infants with no clinical evidence of pulmonary hypertension (Group III) had a mean T 1/2 of 457 ± 66 msec (GM = 453 msec). With the Duncan multirange test, the mean T 1/2 values of Groups I and III and Groups II and III were significantly different ($P < 0.01$). The mean T 1/2 values of infants with evidence of pulmonary hypertension (Groups I and II) were not significantly different ($P < 0.05$). In four patients studied serially, the mean T 1/2 decreased from 649 ± 102 msec to 446 ± 18 msec (GM = 445 msec) after resolution of the pulmonary hypertension. The latter mean was not significantly different from the mean for Group III.

Discussion

Systemic vascular resistance in pulmonary hypertension: The aortic diastolic time constants were significantly different in infants with and without pulmonary hypertension. The most likely explanation for this difference is that patients with pulmonary hypertension have increased systemic vascular resistance as well as increased pulmonary vascular resistance.

The rate of aortic diastolic pressure decay is a reflection of passive events in the arterial circulation during diastole and is primarily dependent on the systemic vascular resistance, aortic compliance and inertance.[9] This pressure decays exponentially according to the first order equation: $P = P_0 e^{-t/\tau}$, where P is the pressure at a given time (t), P_0 is the initial pressure and τ is the aortic diastolic pressure time constant. Solving this equation for T 1/2, when P/P_0 equals 0.5, yields a T 1/2 of 0.693τ. Bourgeois et al.[9] evaluated the aortic diastolic pressure time constant in dogs with no ductus arteriosus shunting and found that it correlated directly with peripheral vascular resistance ($r = 0.9$). Changes in the arterial capacitive component did not significantly affect this constant.

Role of the ductus arteriosus: In the neonate, the ductus arteriosus may be widely patent. Under these circumstances the systemic vascular resistance (R_S) functions as a parallel resistor to the combined pulmonary and ductus arteriosus resistances (R_P and R_D). The latter two resistances function as resistors in series. These relations may be clarified by examining an electric analog model of the circulation (Fig. 1). During systole, the aortic capacitor is charged by the pulse wave generator, the left ventricle. During diastole, the aortic valve is closed, left ventricular output ceases and flow in diastole occurs as the aortic capacitor discharges, causing flow to continue through the parallel resistors described. Assuming that changes in the compliances do not significantly affect the aortic diastolic pressure time constant in the neonate, the aortic diastolic half-life is primarily dependent on and directly proportional to the total resistance (R_I) in the system. Total resistance can be determined from the equation: $1/R_T = 1/R_S + 1/(R_D + R_P)$. This equation may enable us to explain the variations in total resistance and therefore T 1/2, which may occur in certain clinical conditions. In the presence of a widely patent ductus arteriosus (reduced ductus arteriosus resistance) with left to right shunting (systemic vascular resistance greater than pulmonary vascular resistance), total resistance is dependent on both systemic and pulmonary vascular resistance. Because the net resistance of parallel resistors is less than the resistance of either considered separately, the T 1/2 is shorter than normal (ductus closed).[11] When the ductus arteriosus closes (ductus arteriosus resistance equal to infinity), total resistance is dependent on and equal to systemic vascular resistance, and the T 1/2 increases. In a previous study,[11] we observed that the mean T 1/2 of 268 msec increased to 445 msec in a group of infants after closure of a ductus arteriosus. The higher value is similar to the mean in our control Group III, which suggests that the ductus arteriosus in this group is also closed.

In patients with pulmonary hypertension and right to left ductus arteriosus shunting (pulmonary vascular resistance greater than systemic vascular resistance; reduced ductus arteriosus resistance) (Group I), we observed a prolonged T 1/2, indicating that total resistance is greater than normal. Because the maximal total resistance must be less than the lowest resistance in a parallel circuit, both pulmonary vascular resistance and systemic vascular resistance must be elevated in these patients.

Patients with pulmonary hypertension without evidence of right to left ductus arteriosus shunting (Group II) had a more prolonged T 1/2, indicating that total resistance is even greater than that in Group I. Because no shunting was demonstrated, the ductus arteriosus was probably closed (ductus arteriosus resistance equal to infinity), total resistance equals systemic vascular resistance, and systemic vascular resistance is high. Alternatively, the ductus arteriosus was patent, but systemic vascular resistance equaled pulmonary vascular resistance and both were markedly elevated.

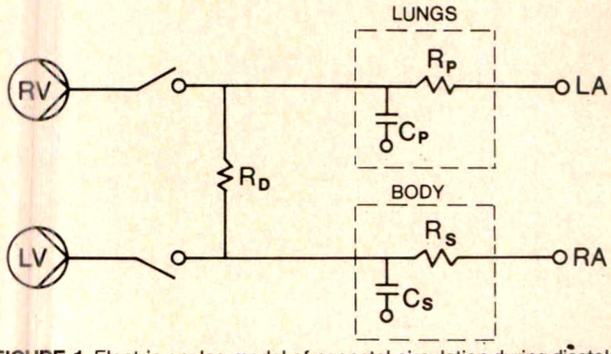

FIGURE 1. Electric analog model of neonatal circulation during diastole. C_s, C_p = capacitance (systemic, pulmonic); LA = left atrium; LV = pulse wave generator (left ventricle); RA = right atrium; RV = pulse wave generator (right ventricle); R_S, R_D, R_P = resistance (systemic, ductal, pulmonary). During systole, C_s is charged by the left ventricular pulse wave generator. The switches indicate that the aortic and pulmonary valves are closed during diastole. C_s then discharges, causing flow to continue both toward R_S and toward R_D and R_P during diastole.

Physiologic implications: The increased systemic vascular resistance in neonates with pulmonary hypertension has important physiologic implications. Systemic vascular resistance primarily reflects peripheral vascular tone. The systemic vasoconstriction observed in infants with pulmonary hypertension could be a primary response to the same mediator influencing the pulmonary vasculature or it could be a compensatory response to maintain systemic blood pressure in the presence of low cardiac output. The cardiac output could be decreased because of either myocardial dysfunction or decreased venous return. Because most of our patients did not have elevated systemic blood pressure, the vasoconstriction responsible for the increased systemic vascular resistance was probably compensatory rather than primary. Whether the increased resistance is a primary or a compensatory response should have important therapeutic implications.

Clinical implications: We found that neonates with pulmonary hypertension have a prolonged aortic diastolic half-life. This finding is most likely due to a concomitant increase in systemic vascular resistance, which has not previously been reported in patients with pulmonary hypertension. The presence of increased systemic vascular resistance in neonates with pulmonary hypertension has important diagnostic and etiologic implications. Finally, aortic diastolic pressure analysis may provide an important tool for assessing systemic vascular resistance or both systemic and pulmonary vascular resistance in the presence of a patent ductus arteriosus.

Acknowledgment

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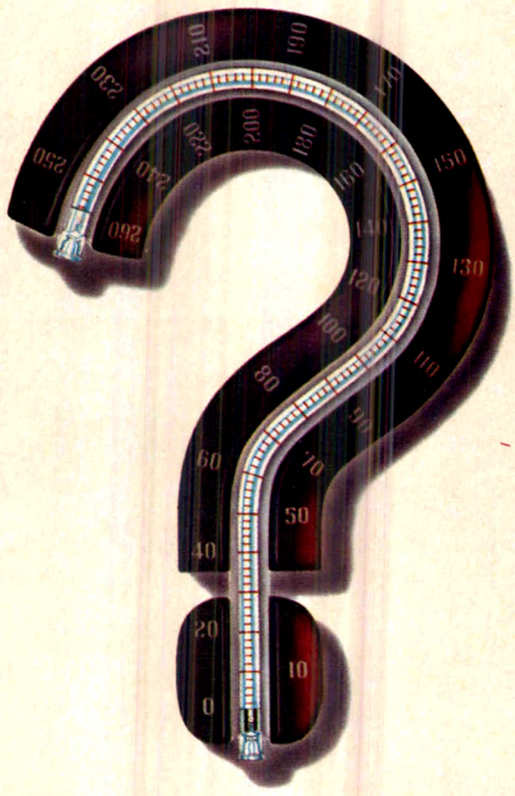

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...ANSWERS ABOUT

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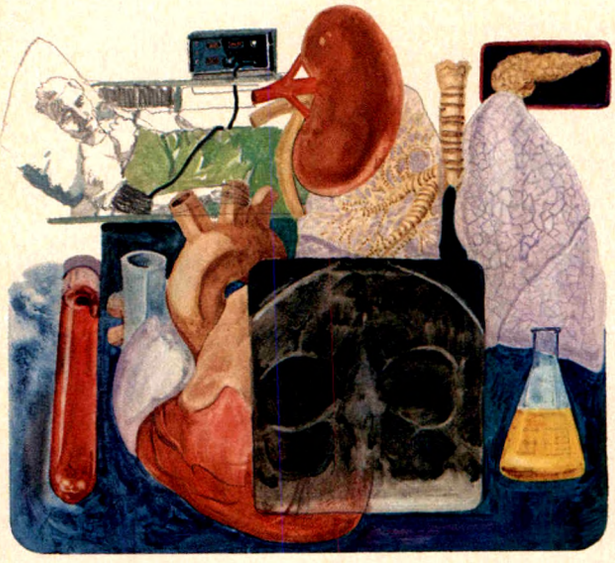

ALDOMET can be used in a wide range of hypertensives, including those with:

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- hyperuricemia
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ALDOMET (Methyldopa, MSD) is contraindicated in active hepatic disease, hypersensitivity to the drug, and if previous methyldopa therapy has been associated with liver disorders.

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Does an antihypertensive lower blood pressure usually without lowering cardiac output?

ALDOMET DOES
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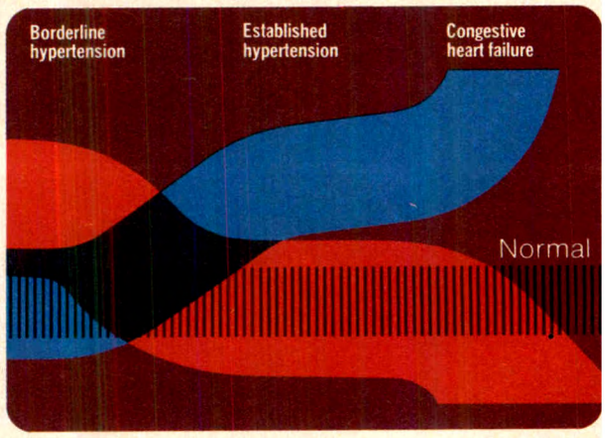
ALDOMET has no direct effect on cardiac function and lowers blood pressure usually without reducing cardiac output. Rather, it appears to reduce peripheral vascular resistance, the most commonly identified hemodynamic variable in hypertension (as hypertension progresses cardiac output tends to decrease and peripheral resistance tends to increase).

Hemodynamic Changes as Hypertension Progresses*



*adapted from Messerli and de Carvalho[1]

This may be particularly important in hypertensives with impaired cardiac function such as those with congestive heart failure.*

*Edema may occur with ALDOMET. This is usually relieved by the use of a diuretic, but if edema progresses methyldopa should be discontinued.

TABLETS: 500 mg, 250 mg, and 125 mg

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The most prescribed nondiuretic antihypertensive in the U.S. today

Can an antihypertensive be effective usually without further reducing renal blood flow?

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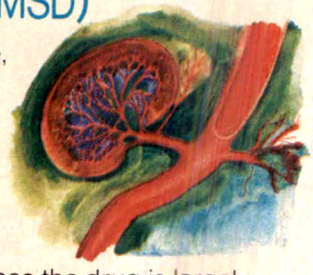

Glomerular filtration rate, filtration fraction, and renal blood flow are usually not reduced; therefore, ALDOMET is appropriate for many hypertensive patients with significantly impaired renal function. Since the drug is largely excreted by the kidney, patients with impaired renal function may respond to smaller doses.

Will an antihypertensive generally allow a normal cardiovascular response to exercise?

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Cardiac output and blood pressure normally increase as the physical activities of the patient increase. ALDOMET does not significantly impair normal fluctuations of blood pressure during exercise.[2,3] This can be of importance to active hypertensive patients—such as athletic individuals or persons whose work requires substantial physical effort. With ALDOMET, exercise hypotension rarely occurs.

Sedation, usually transient, may occur during the initial period of therapy or whenever the dose is increased. Headache, asthenia, or weakness may be noted as early and transient symptoms.

Has an antihypertensive shown a proven record in long-term therapy?

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A recent study[4] followed a group of patients on ALDOMET for ten years or more. The results suggest that ALDOMET is a highly effective medication for the long-term management of hypertension.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed.

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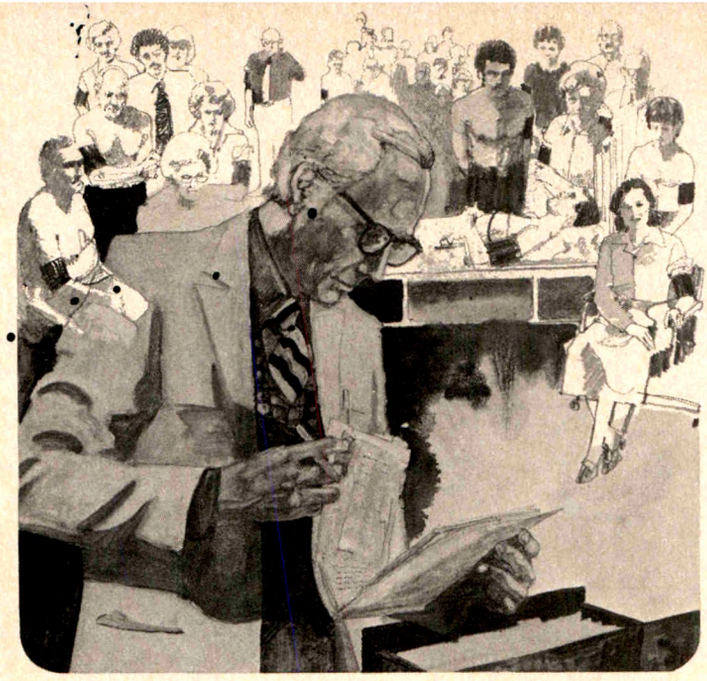

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Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the *red cell* is usually coated with gamma globu*lin of the* IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, occasionally with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant or intend to nurse requires that anticipated benefits be weighed against possible risks; possibility of fetal injury or injury to a nursing infant cannot be excluded. Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced dose
anesthetics; hypotension occurring during ar
thesia usually can be controlled with vasopress
Hypertension has recurred after dialysis in pati
on methyldopa because the drug is removed by
procedure.

Adverse Reactions: *Central nervous system:* Se
tion, headache, asthenia or weakness, usually e
and transient; dizziness, lightheadedness, sy
toms of cerebrovascular insufficiency, paresthes
parkinsonism, Bell's palsy, decreased mental ac
involuntary choreoathetotic movements; psy
disturbances, including nightmares and revers
mild psychoses or depression.

Cardiovascular: Bradycardia, aggravation of an
pectoris. Orthostatic hypotension (decrease
dosage). Edema (and weight gain) usually relieve
use of a diuretic. (Discontinue methyldopa if ed
progresses or signs of heart failure appear.)

Gastrointestinal: Nausea, vomiting, distention,
stipation, flatus, diarrhea, mild dryness of mo
sore or "black" tongue, pancreatitis, sialadenit

Hepatic: Abnormal liver function tests, jaun
liver disorders.

Hematologic: Positive Coombs test, hemolytic
mia. Leukopenia, granulocytopenia, thrombo
penia. Positive tests for antinuclear antibody
cells, and rheumatoid factor.

Allergic: Drug-related fever, lupus-like syndr
myocarditis.

Other: Nasal stuffiness, rise in BUN, breast enl
ment, gynecomastia, lactation, impotence,
creased libido, dermatologic reactions inclu
eczema and lichenoid eruptions, mild arthra
myalgia.

Note: Initial adult dosage should be limite
500 mg daily when given with antihyperten
other than thiazides. Tolerance may occur, us
between second and third months of the
increased dosage or adding a diuretic frequ
restores effective control. Patients with imp
renal function may respond to smaller d
Syncope in older patients may be related to incre
sensitivity and advanced arteriosclerotic vas
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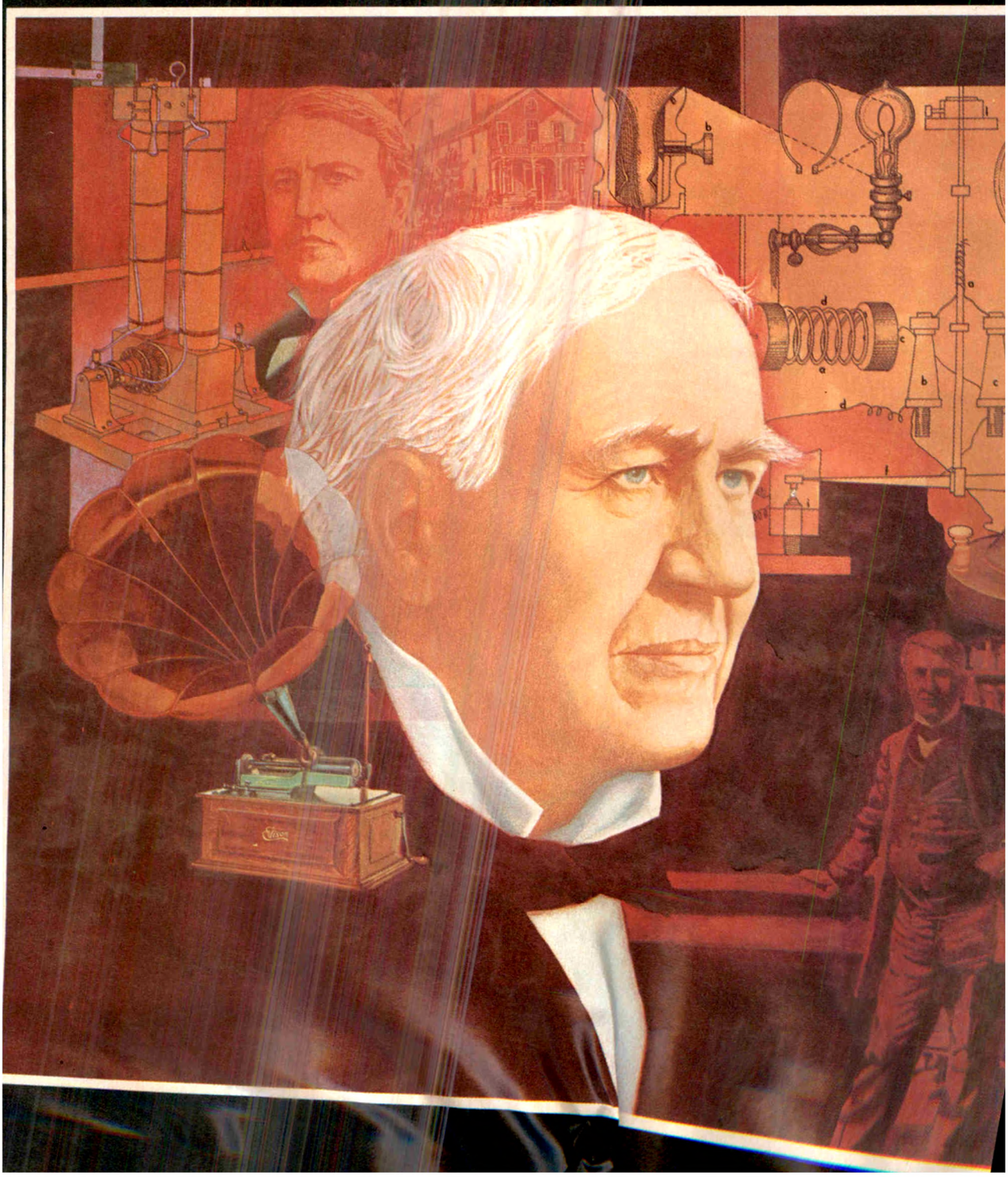

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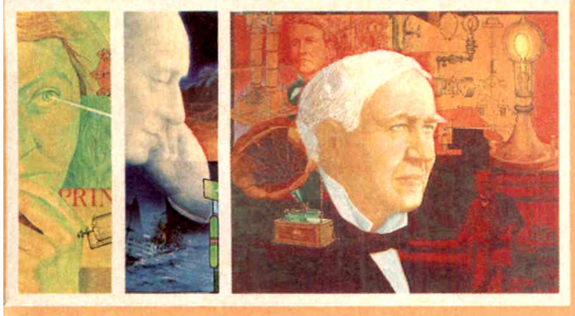
This unparalleled range of programmable features made possible by custom CMOS (complementary oxide-semiconductor) integrated circuitry, recognize its high reliability and low power consumption.

CyberLith functions may be programmed individu or in combination, using a battery-powered portable grammer. Reprogramming is automatically confirmed and an advanced fail-safe feature guards against accide tal reprogramming.

The CyberLith. A system that Thomas Edison would admire.

Contact your Intermedics Representative for additional information on the many other advantages of our multi-programmable CyberLith Pacing System.

At Intermedics, we are producing tomorrow's technology today, because OUR BUSINESS IS LIFE.



Free limited edition print offer from Intermedics, Inc.

The Thomas Edison original water color is the third in a series by artist Ron Adair, commissioned by Intermedics. A limited-edition print, numbered and signed by the artist, is available to physicians only from Intermedics. To obtain your print, please write to Marketing Administration, Intermedics, Inc., P.O. Box 617, Freeport, Texas 77541.

NOTE: The CyberLith is currently undergoing clinical evaluation and is not routinely available on a commercial basis.

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Intermedics Pulse Generators

INDICATIONS FOR USE Implantable cardiac pulse generators may be indicated for long-term treatment of impulse formation or conduction disorders resulting in symptomatic bradyarrhythmias, tachyarrhythmias, and heart block unresponsive to drug therapy.

PRECAUTIONS Implanted pacemakers have a finite and variable service life as a result of factors such as the initial capacity of the battery and the shelf storage time of the manufactured pacemaker; variations in electrode system resistances, stimulation rate, and the percentage of time the implanted pacemaker is inhibited; and random electronic component failures.

Pacemaker operation can be influenced by electric, magnetic, or electromagnetic energy mimicking normal cardiac activity. In addition, certain environmental sources can couple sufficient energy into a pacemaker system to damage the pulse generator. Specifically, diathermy should not be used on pacemaker patients because of possible total inhibition of the pulse generator; electrocautery can inhibit and/or damage the pacemaker as well as cause burns or possible ventricular fibrillation; defibrillation can damage the pacemaker, and the presence of the pacemaker may cause increased cardiac muscle damage from defibrillation. Microwave ovens that do not exceed federal guidelines for leakage (0.5 W/cm^2 at 2.5 cm from the appliance) will not affect the pacemaker, but leakage in excess of that amount may cause interference. Certain electrical and gasoline-powered appliances can cause inhibition of an implanted cardiac pacemaker system.

For complete precautions, see the Physician's Manual for the Intermedics cardiac pulse generator to be used.

CONTRAINDICATIONS AND SIDE EFFECTS There are no known contraindications to the use of pacemakers as a medical method for control of heart rate. Body rejection phenomena, local tissue reaction or skin necrosis, muscle and nerve stimulation, embolism, and cardiac tamponade have been reported.

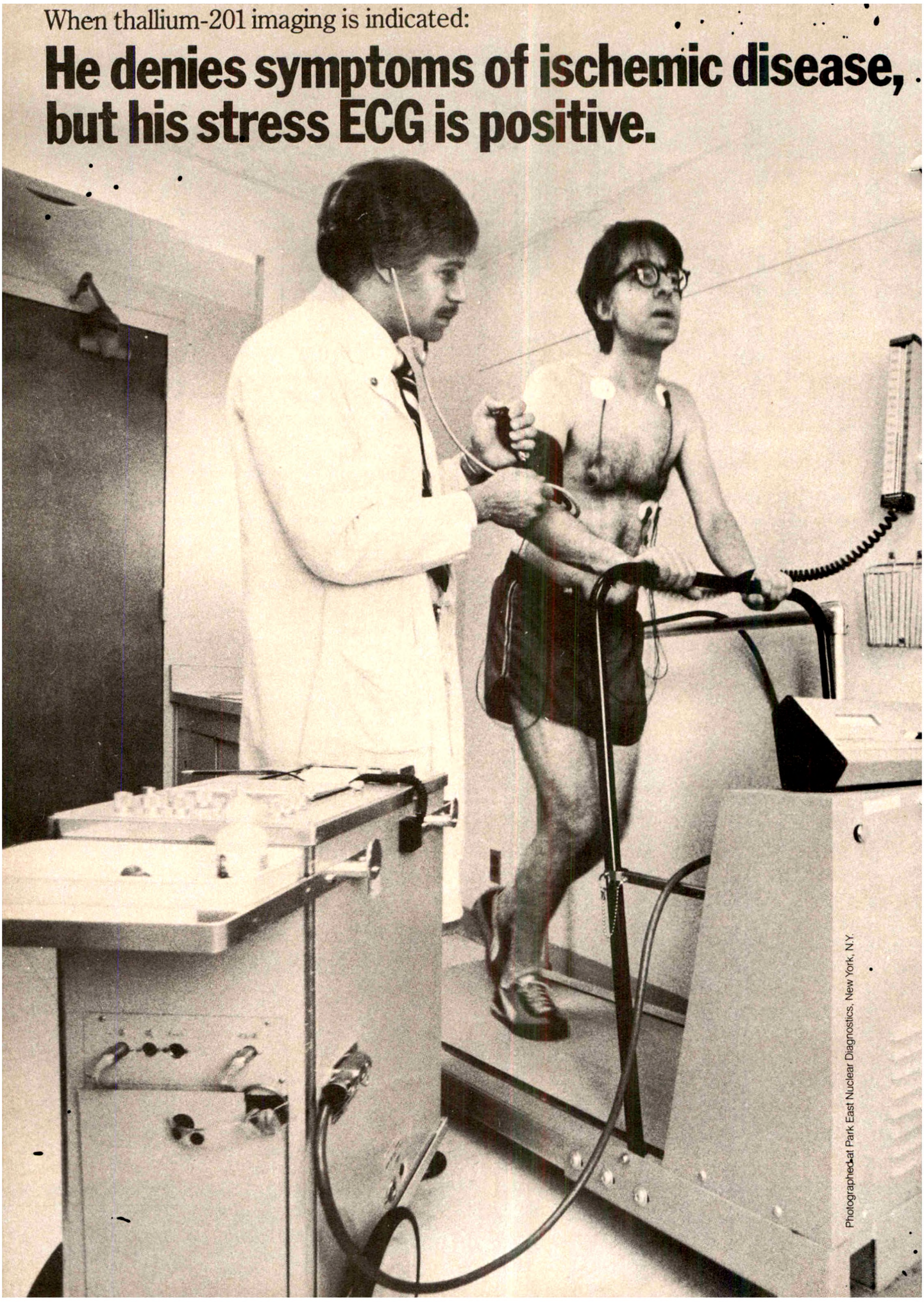
Intermedics Inc.

P.O. Box 617 Freeport, Texas 77541
Tel: (713) 233-8611
Toll free: 1-800-231-2330

Our business is life.™

When thallium-201 imaging is indicated:

He denies symptoms of ischemic disease, but his stress ECG is positive.



Photographed at Park East Nuclear Diagnostics, New York, N.Y.

The stress ECG, once restricted to evaluation of symptomatic patients with suspected myocardial ischemia, has seen recent application in screening selected high-risk *asymptomatic* patients... airline flight crews, executives applying for corporate insurance policies and physical conditioning programs, security officials, and others.

However, 30% of asymptomatic patients with angiographically documented absence of significant coronary artery disease have false-positive stress tests.[1,2] Positive ECGs in such asymptomatic patients present a clinical management challenge: How much significance should be attributed to these findings? Although angiography can confirm absence of significant disease, many clinicians may hesitate to perform such an invasive procedure on asymptomatic patients in order to differentiate false from true positives.

Noninvasive thallium-201 imaging performed as an adjunct to the stress ECG can significantly enhance the specificity and sensitivity of electrocardiographic studies. Intravenously injected thallium-201 is taken up like potassium and concentrated most avidly by normal, well-perfused myocardial cells. Ischemic myocardial cells take up less thallium-201 – in proportion to the decrease in blood flow – particularly during maximal stress, when the differential in perfusion is most marked between regions supplied by normal coronary arteries and those supplied by stenotic vessels. Routinely available nuclear medicine imaging equipment can record any regional differences in thallium-201 uptake – and thus in myocardial perfusion – confirming the presence or absence of coronary disease.

Thallium imaging in conjunction with stress electrocardiography has proved to be a highly sensitive means of detecting CAD. In asymptomatic patients with a positive stress ECG, the specificity has approached 100%.[3]

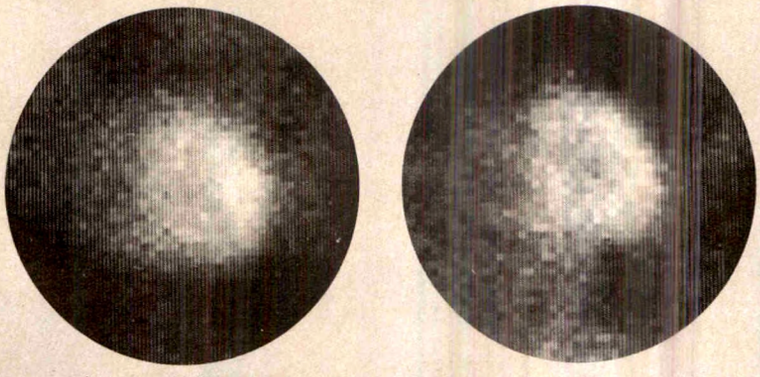
When an asymptomatic patient in your practice presents with positive stress ECG findings – consider a repeat stress study with thallium-201. Both research results and clinical experience have demonstrated that the combination of thallium-201 cardiography and the stress ECG can

- detect single-vessel disease in advance of electrocardiographic evidence[4]
- increase the sensitivity and specificity of the stress ECG, particularly in patients where ECG findings and symptomatology do not agree[5,6,7]
- identify those patients with clinically significant but electrically silent coronary disease – patients who will clearly need angiographic evaluation[7]

Unlike angiography, which displays the static anatomic details of the major coronary vessels, thallium imaging directly demonstrates – in a dynamic manner – the response of regional myocardial blood flow to coronary stenosis. Redistribution of thallium occurs over time into viable myocardium, representing stress-induced reversible ischemia, but not into regions of previous scar formation. Thus, initial perfusion defects that "fill in" on later images represent regions of viable myocardium that may benefit from medical or surgical control.

For asymptomatic patients with a positive stress ECG, the findings of a stress thallium-201 myocardial perfusion study may either rule out significant coronary stenosis, or provide a sound clinical basis for more invasive diagnostic evaluation.[6]

1. Bartel AG et al: Graded exercise stress test in angiographically documented coronary artery disease. *Circulation* **49**:348, 1974.
2. Goldschlager N et al: Treadmill stress tests as indicators of presence and severity of coronary artery disease. *Ann Intern Med* **85**:277, 1976.
3. Berman DS et al: Exercise myocardial scintigraphy with thallium-201: Evaluation of asymptomatic patients with positive treadmill electrocardiograms. Proceedings of the Western Regional Society of Nuclear Medicine Meeting, Las Vegas, October 1977.
4. Bailey IK et al: Thallium-201 myocardial perfusion imaging at rest and during exercise. Comparative sensitivity to electrocardiography in coronary artery disease. *Circulation* **55**:79, 1977.
5. Blood DK et al: Comparison of thallium-201 myocardial scans at rest with scans four hours after exercise. *Circulation* **56** (suppl 3): 229, 1977.
6. Raphael LD et al: Thallium exercise myocardial scintigraphy in patients with "angina and normal coronary arteriograms" (abs). *Circulation* **53-54** (suppl 2): 217, 1976.
7. Ritchie JL et al: Myocardial imaging with thallium-201 at rest and during exercise. Comparison with coronary arteriography and resting and stress electrocardiography. *Circulation* **56**:66, 1977.



Anterior thallium studies of 45-year-old male with positive exercise ECG but no symptoms of stress-induced ischemia. Postexercise image (left) reveals inferior-wall perfusion deficit. Image made 4 hours later (right) demonstrates reperfusion, confirms presence of coronary disease.

Thallous Chloride Tl 201

NEN New England Nuclear®

Please see following page for brief prescribing information.

Thallous Chloride Tl 201

For Diagnostic Use

November 1977

Indications and Usage: Thallous Chloride Tl 201 may be useful in myocardial perfusion imaging for the diagnosis and localization of myocardial infarction.

It may also be useful in conjunction with exercise stress testing as an adjunct in the diagnosis of ischemic heart disease (atherosclerotic coronary artery disease).

Contraindications: None known.

Warnings: In studying patients in whom myocardial infarction or ischemia is known or suspected, care should be taken to assure continuous clinical monitoring and treatment in accordance with safe, accepted procedure. Exercise stress testing should be performed only under the supervision of a qualified physician and in a laboratory equipped with appropriate resuscitation and support apparatus.

Ideally, examinations using radiopharmaceutical drug products—especially those elective in nature—of women of childbearing capability should be performed during the first ten days following the onset of menses.

Precautions: Data are not available concerning the effect of marked alterations in blood glucose, insulin, or pH (such as is found in diabetes mellitus) on the quality of thallium Tl 201 scans. Attention is directed to the fact that thallium is a potassium analog, and since the transport of potassium is affected by these factors, the possibility exists that the thallium may likewise be affected.

Thallous Chloride Tl 201, as all radioactive materials, must be handled with care and used with appropriate safety measures to minimize external radiation exposure to clinical personnel. Care should also be taken to minimize radiation exposure to patients in a manner consistent with proper patient management.

No long-term animal studies have been performed to evaluate carcinogenic potential.

Adequate reproduction studies have not been performed in animals to determine whether this drug affects fertility in males or females, has teratogenic potential, or has other adverse effects on the fetus. Thallous Chloride Tl 201 should be used in pregnant women only when clearly needed.

It is not known whether this drug is excreted in human milk. As a general rule nursing should not be undertaken when a patient is administered radioactive material.

Safety and effectiveness in children have not been established.

Adverse Reactions: Adverse reactions related to use of this agent have not been reported to date.

Dosage and Administration: The recommended adult (70kg) dose of Thallous Chloride Tl 201 is 1-1.5mCi. Thallous Chloride Tl 201 is intended for intravenous administration only.

For patients undergoing resting thallium studies, imaging is optimally begun within 10-20 minutes after injection. Several investigators have reported improved myocardial-to-background ratios when patients are injected in the fasting state, in an upright posture, or after briefly ambulating.

Best results with thallium imaging performed in conjunction with exercise stress testing appear to be obtained if the thallium is administered when the patient reaches maximum stress and when the stress is continued for 30 seconds to one minute after injection. Imaging should begin within ten minutes post-injection since target-to-background ratio is optimum by that time. Several investigators have reported significant decreases in the target-to-background ratios of lesions attributable to transient ischemia by two hours after the completion of stress testing.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

Radiopharmaceuticals should be used by persons with specific training in the safe use and handling of radionuclides produced by nuclear reactor or particle accelerator and whose experience and training have been approved by the appropriate government agencies authorized to license the use of radionuclides.

How Supplied: Thallous Chloride Tl 201 for intravenous administration is supplied as a sterile, non-pyrogenic solution containing at calibration time, 1mCi/ml of Thallous Tl 201, 9mg/ml sodium chloride, and 9mg/ml of benzyl alcohol. The pH is adjusted to between 4.5-6.5 with hydrochloric acid and/or sodium hydroxide solution. Vials are available in the following quantities of radioactivity: 1.5, 3.0, 4.5, 6.0, and 9.0 millicuries of Thallous Tl 201.

The contents of the vial are radioactive. Adequate shielding and handling precautions must be maintained.

Catalog Number NRP-427

New England Nuclear
Medical Diagnostics Division
601 Treble Cove Rd., North Billerica, MA 01862

Call Toll-Free: 800-225-1572 / Telex: 94-0996
(In Mass. and International: 617-482-9595)

Canada: NEN Canada, 2453 46th Avenue, Lachine, Que. H8T 3C9
Tel: 514-636-4971
Europe: NEN Chemicals GmbH, D-6072 Dreieich, W. Germany, Postfach 401240
Tel: (06103) 85034 Order Entry: (06103) 81013

FOR DEEP INTRAMUSCULAR INJECTION ONLY.

Indications: In treatment of infections due to penicillin G-sensitive microorganisms susceptible to the low and very prolonged serum levels common to this dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and clinical response.

The following infections usually respond to adequate dosage of IM penicillin G benzathine.

Streptococcal infections (Group A—without bacteremia). Mild to moderate upper respiratory infections (e.g., pharyngitis).

Venereal infections —Syphilis, yaws, bejel, and pinta.

Medical conditions in which penicillin G benzathine therapy is indicated as prophylaxis:

Rheumatic fever and/or chorea —Prophylaxis with penicillin G benzathine has proven effective in preventing recurrence of these conditions. It has also been used as followup prophylactic therapy for rheumatic heart disease and acute glomerulonephritis.

Contraindications: Previous hypersensitivity reaction to any penicillin.

Warnings: Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported. Anaphylaxis is more frequent following parenteral therapy but has occurred with oral penicillins. These reactions are more apt to occur in individuals with history of sensitivity to multiple allergens. Severe hypersensitivity reactions with cephalosporins have been well documented in patients with history of penicillin hypersensitivity. Before penicillin therapy, carefully inquire into previous hypersensitivity to penicillins, cephalosporins and other allergens. If allergic reaction occurs, discontinue drug and treat with usual agents, e.g., pressor amines, antihistamines and corticosteroids.

Precautions: Use cautiously in individuals with histories of significant allergies and/or asthma.

Carefully avoid intravenous or intraarterial use, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage.

In streptococcal infections, therapy must be sufficient to eliminate the organism, otherwise the sequelae of streptococcal disease may occur. Take cultures following completion of treatment to determine whether streptococci have been eradicated.

Prolonged use of antibiotics may promote overgrowth of non-susceptible organisms including fungi. Take appropriate measures if superinfection occurs.

Adverse Reactions: Hypersensitivity reactions reported are skin eruptions (maculopapular to exfoliative dermatitis), urticaria and other serum sickness-like reactions, laryngeal edema and anaphylaxis. Fever and eosinophilia may frequently be only reaction observed. Hemolytic anemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent and usually associated with high parenteral doses.

As with other antisyphilitics, Jarisch-Herxheimer reaction has been reported.

Composition: (units penicillin G benzathine as active ingredient in aqueous suspension): 300,000 units per ml—10-ml multi-dose vial. Each ml also contains sodium citrate buffer, approximately 6 mg lecithin, 3 mg povidone, 1 mg carboxymethylcellulose, 0.5 mg sorbitan monopalmitate, 0.5 mg polyoxyethylene sorbitan monopalmitate, 1.2 mg methylparaben and 0.14 mg propylparaben.

600,000 units in 1-ml TUBEX® (sterile cartridge-needle unit) Wyeth, packages of 10.

900,000 units, 1.5-ml fill in 2-ml TUBEX, packages of 10.

1,200,000 units in 2-ml TUBEX, packages of 10, and in 2-ml single-dose disposable syringe, packages of 10.

2,400,000 units in 4-ml single-dose disposable syringe, packages of 10.

Each TUBEX or disposable syringe also contains sodium citrate buffer and, as w/v, approximately 0.5% lecithin, 0.6% carboxymethylcellulose, 0.6% povidone, 0.1% methylparaben and 0.01% propylparaben.

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INJECTION

BICILLIN® L-A

(STERILE PENICILLIN G BENZATHINE SUSPENSION)

Wyeth Laboratories
Philadelphia, Pa. 19101

GUESS WHAT PROTECTION HE'LL FORGET TO TAKE.

For rheumatic fever prophylaxis he can't forget:

Injection penicillin G benzathine is the recommended drug of choice* to prevent streptococcal infection and possible recurrence of rheumatic fever. One injection, once a month, of 1,200,000 units usually offers effective and continuous prophylaxis, virtually eliminating the problem of patient compliance.

*Commission on Rheumatic Fever and Bacterial Endocarditis of the Council on Cardiovascular Disease in the Young: "Rheumatic Fever Prevention," 71-006-B. American Heart Association, New York, (Sept.) 1976.

INJECTION

BICILLIN® L-A

(STERILE PENICILLIN G BENZATHINE SUSPENSION)

Wyeth Laboratories
Philadelphia, Pa. 19101

◀ See important information on preceding page.

CRYSTAL CONTROLLED ACCURACY...CARDIOTEST™

Crystal-controlled timing makes CARDIOTEST today's wisest choice in pacemaker test instruments. And its extra capabilities will allow CARDIOTEST to test tomorrow's pacemakers too. For effective pacemaker evaluation, you need a system tester more accurate and more precise than the device tested — CARDIOTEST.

VERSATILITY. CARDIOTEST is a three-in-one instrument which tests implantable pacers, measures threshold parameters and tests implanted pacers noninvasively.

ACCURACY. Threshold Testing: The CARDIOTEST pulse generator approximates the function of an implanted unit, for closer simulation of pulse generator performance. A variable sensitivity feature allows the full range from demand to asynchronous pacing.

Implantable Pacer Testing: CARDIOTEST sensitivity measurements are uniquely precise. Unlike competitors' testers, CARDIOTEST gives the implanting physician the assurance that sensitivity is adequate at implant time. Voltage is measured at midpoint — a more accurate representation of real output pulse energy than at other points in the pulse. Because of this distinctive midpoint-measurement feature, CARDIOTEST can measure voltage over the various pulse widths available with today's pulse width programmable pacemakers.

SECURITY. By testing the pacemaker with CARDIOTEST prior to implant, the physician can document the device's proper function, without introducing more test equipment to the operating room.

EASE OF USE. Pushbutton operation and compactness make this the most "human engineered" test instrument available. Bright, readable digital display can be seen from across the room — and LED indicators tell which parameter is being measured. Easy to measure resistance — just push the button. No need to measure slew rate — CARDIOTEST's electronic bandpass filter compensates for frequency content of the R-wave.

CPI® Meets Your Needs.

DISPLAY AREA —
LED Digital Display
LED Measurement Indicators
PACE and SENSE LED Indicators
Battery Low LED Indicator

THRESHOLD TEST DEVICE —
Control dials for adjusting rate, pulse width, voltage and sensitivity (asynchronous to full demand) parameters during patient pacing and threshold measurements.

Pushbutton selectors for rate, pulse width, voltage and resultant current, resistance and cardiac R-wave measurements.

PACER TEST DEVICE —
Pushbutton selectors for rate, pulse interval, pulse width, voltage, paced and sensed refractory periods, and positive and negative R-wave sensitivity measurements of external or implantable pulse generators.

NONINVASIVE TEST DEVICE —
Pushbutton selectors for rate, pulse interval and pulse width measurements of an implanted pacemaker.

Cardiac Pacemakers, Inc.
4100 North Hamline Avenue
P.O. Box 43079
St. Paul, Minnesota 55164, U.S.A.

INVOLVED IN MANKIND

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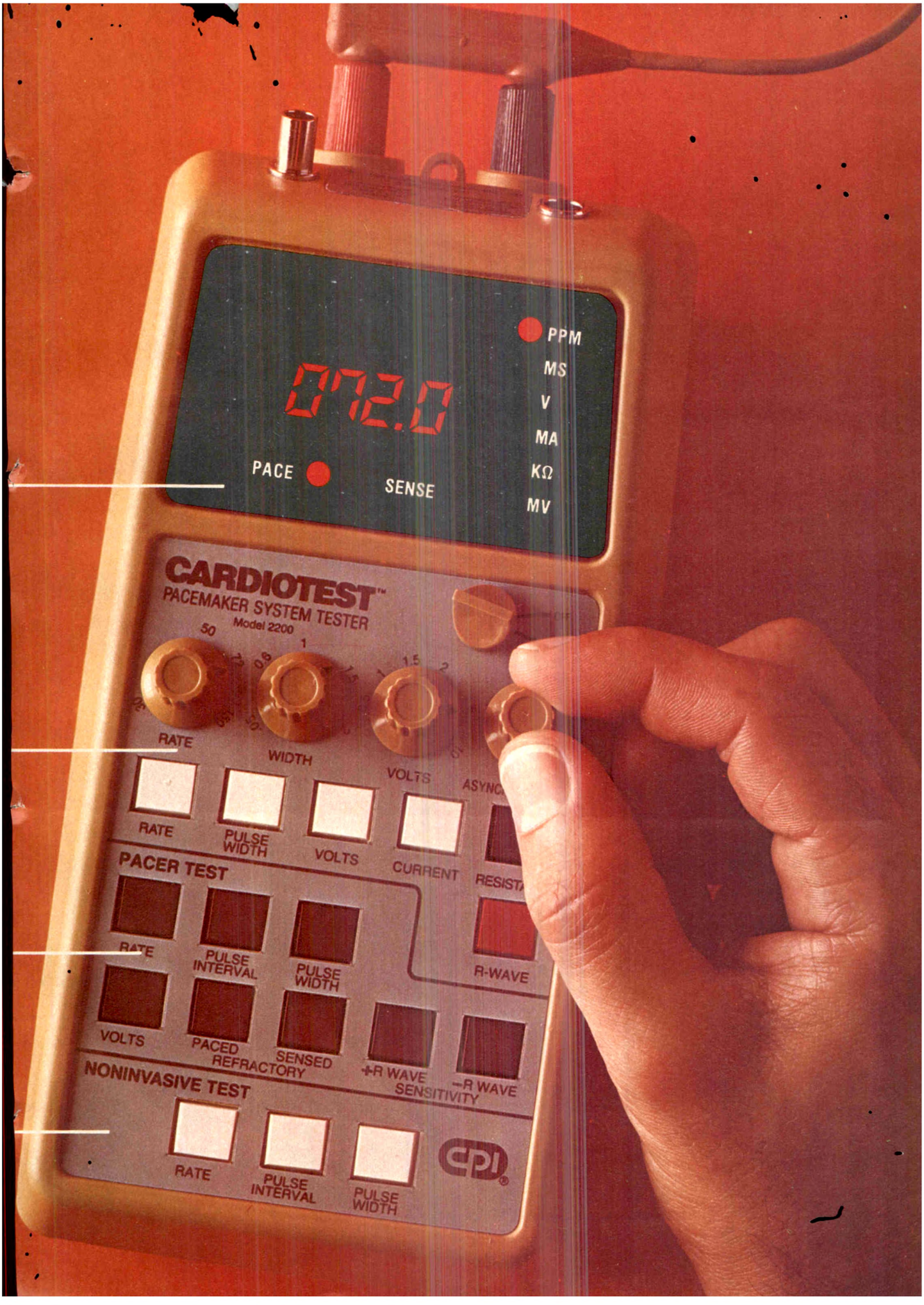
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PULSE INTERVAL
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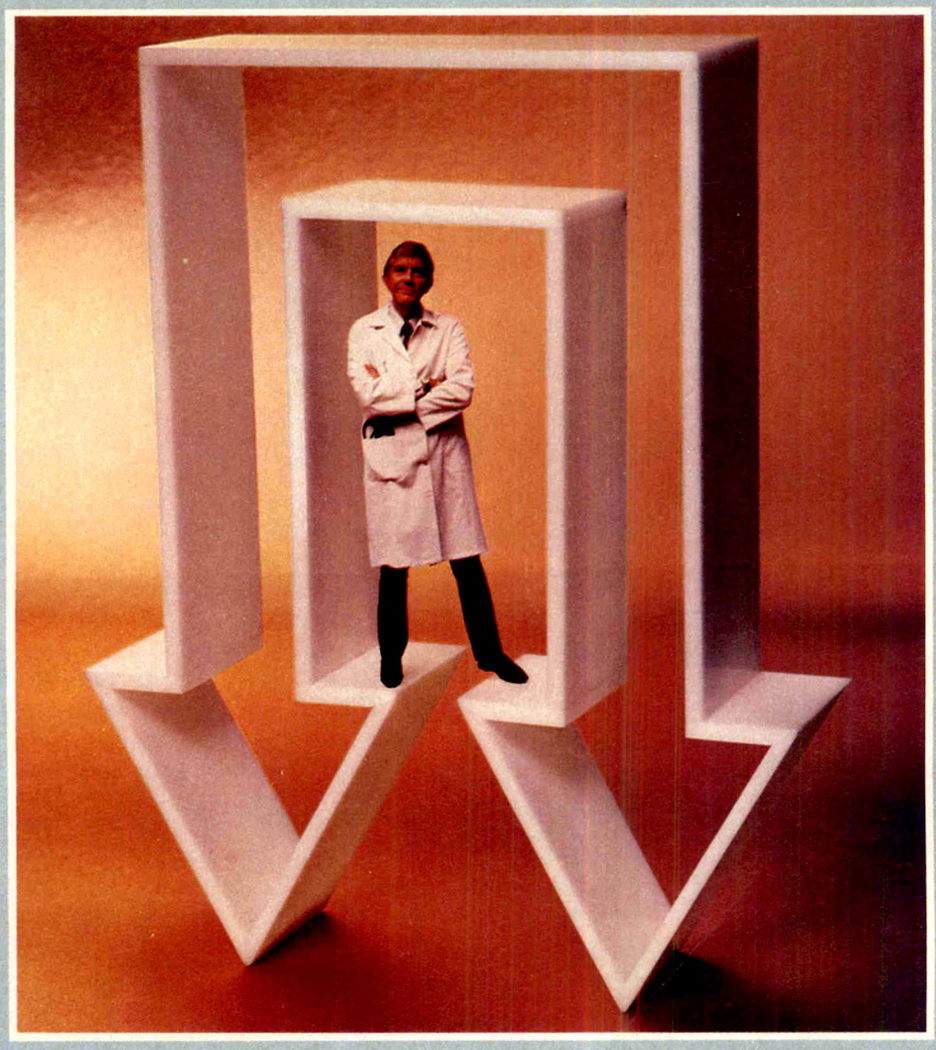
A "First-Step" Agent for Your Hypertensive Patient

SELACRYN®

brand of **ticrynafen** 250 mg. Tablet

Usual Dosage: Once a Day



Lowers Blood Pressure

Lowers Uric Acid

Important Benefits for Your Hypertensive Patient

'Selacryn' provides: Three desirable clinical effects in a single agent—antihypertensive, diuretic, uricosuric; Proven once daily round-the-clock antihypertensive control, helping you provide a simplified regimen; Appropriate in primary hypertension regardless of severity, 'Selacryn' is compatible with nondiuretic antihypertensives; Similar to hydrochlorothiazide in effect on electrolytes, no special replacement measures are ordinarily required; and Effective reduction of uric acid levels.

Prescribe 'Selacryn' with Confidence
In most respects, the type, incidence and severity of adverse reactions seen with 'Selacryn' are similar to those seen with thiazides over the years. Standard laboratory tests you use to monitor the course of thiazide therapy are indicated when you prescribe 'Selacryn'.

Discontinue Previous Diuretics
In hypertensive patients, discontinue any previous diuretics for three days before instituting 'Selacryn'. Where feasible, in patients with congestive cardiac failure, discontinue the other diuretic for one to two days before beginning 'Selacryn'. Occasionally, in patients switched from other diuretics without a washout period, nausea, vomiting, flank pain, azotemia, oliguria and, rarely, anuria have been reported.

Maintain Adequate Fluid Intake and Urine Flow with Initial Doses
For patients switched to 'Selacryn' from other diuretics (see above), and for dehydrated patients, hydration is recommended for three days before and three days after starting 'Selacryn'. Since initial doses of 'Selacryn' produce diuresis as well as uricosuria, urinary uric acid concentration does not increase in well-hydrated patients who can increase urine flow.

Reduce Dosage of Concomitant Anticoagulants
'Selacryn' potentiates oral anticoagulants; use caution when using these drugs together. In such patients, reduce the oral anticoagulant to one-quarter or one-half the maintenance dose, monitor prothrombin time through titration until stabilized.

Potassium Supplements Are Usually Not Necessary
but may be advisable in some patients. Since some patients who received 'Selacryn' and Dyrenium® (brand of triamterene) have shown marked elevation of BUN and creatinine, such a combination is not recommended.

See next page for indications and brief summary of prescribing information.

SELACRYN®
brand of ticrynafen 250 mg. Tablet

Logical Successor to Thiazide in First-Step Management

SK&F
a SmithKline company

© Smith Kline & French Laboratories, 19

SELACRYN®

brand of ticrynafen 250 mg. Tablet

Before prescribing, see complete prescribing information in SK&F literature. The following is a brief summary.

Indications: Hypertension, with or without elevated uric acid levels. Salt and water retention states associated with congestive cardiac failure.

Contraindications: Anuria, severe or progressive renal disease, hypersensitivity to the drug, known renal uric acid calculi.

Warnings: Potentiates the action of oral anticoagulants; caution should be exercised when these agents are used with 'Selacryn'; reduce anticoagulant dosage to 1/4 or 1/2 of the maintenance dose, and carefully monitor prothrombin time until stabilized.

Concomitant use with triamterene is not recommended since a marked elevation of BUN and creatinine may occur.

Not appropriate in hepatic ascites. May precipitate azotemia in progressive or advanced renal disease; therefore, frequent electrolyte, creatinine and BUN determinations should be performed early in therapy and periodically thereafter. Discontinue the drug if renal impairment progresses.

Pregnancy, Nursing: 'Selacryn' crosses the placental barrier in animals. Routine use of diuretics during normal pregnancy is inappropriate and exposes mother and fetus to unnecessary hazard. Use in pregnancy requires weighing anticipated benefits against possible hazards. Generally, nursing should not be undertaken while a patient is on a drug.

Precautions: Substantial uricosuria occurs within hours after the first dose of 'Selacryn'; for this reason, hypertensive patients switching from other diuretics should discontinue diuretics for 3 days before starting 'Selacryn'; where feasible, diuretics should be discontinued for 1 to 2 days in patients with congestive cardiac failure. Fluid intake should be increased to approximately 1500 cc. per day for up to 3 days before and 3 days after initiation of 'Selacryn' therapy in patients switched to 'Selacryn' from other diuretics and in patients who may be dehydrated, particularly if the patients are hyperuricemic.

Acute attacks of gout may be precipitated; continue 'Selacryn' (brand of ticrynafen), add colchicine. Observe patients for signs of electrolyte imbalance, i.e., hypokalemia, hyponatremia, hypochloremic alkalosis. Periodic determinations of electrolytes to detect possible imbalance should be performed. Concomitant use with cytotoxic agents requires caution and individualization of dosage and management. Effects on glucose metabolism are similar to those seen with thiazides. Insulin requirements may be affected; hyperglycemia and glycosuria may occur in patients with latent diabetes. Elevation of BUN and/or serum creatinine can occur during diuretic therapy.

Children: Safety and effectiveness in children have not been established.

Drug Interactions: Exercise caution when administering with other highly protein-bound drugs, especially anticoagulants; reduce anticoagulant dose to 1/4 or 1/2 of the maintenance dose and carefully monitor prothrombin time until stabilized. (See Warnings.) Concomitant use with triamterene is not recommended since a marked elevation of BUN and creatinine may occur.

The drug causes a decrease in excretion of salicylates and organic acids, e.g., penicillin. Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Adverse reactions seen with 'Selacryn' (brand of ticrynafen) in controlled studies were approximately the same as those seen with hydrochlorothiazide. Except where noted, the following adverse effects seen with 'Selacryn' have been reported in a small number of patients, e.g., approximately 1 in 100: anorexia, nausea, vomiting, dyspepsia, cramping, diarrhea, constipation, headache (approximately 4 in 100), dizziness/lightheadedness (approximately 9 in 100), paresthesia, somnolence, insomnia, syncope, vertigo, orthostatic hypotension, palpitation, rash, urticaria, pruritus, rare cases of fever and interstitial nephritis. Tiredness/fatigue (approximately 4 in 100), hyperglycemia, glycosuria, muscle cramps, weakness, bitter taste and dryness in mouth, exacerbation of gout, renal colic or costovertebral pain. Abnormal liver function tests and jaundice have been reported in a few patients.

Occasionally, patients who received 'Selacryn' without a washout period (See Precautions) experienced nausea, vomiting, flank pain, azotemia, oliguria and, rarely, anuria; these effects were reversible.

The following adverse reactions have not been reported to date with 'Selacryn' but have occurred with thiazides or other diuretics: pancreatitis, sialadenitis, xanthopsia, purpura, photosensitivity, necrotizing angiitis, Stevens-Johnson syndrome, respiratory distress, anaphylactic reaction, leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, restlessness and transient blurred vision.

Supplied: Light blue, round, scored, monogrammed tablets of 250 mg. in bottles of 100, and in Single Unit Packages of 100 (intended for institutional use only).

Date of issuance Sept. 1979

Smith Kline & French Laboratories
Philadelphia, Pa.

Quantitative MB/CPK results STAT any time of day or night

Know without delay whether myocardial infarction has occurred. The new Lancer MB/CPK Separation System ends your long wait for isoenzyme information while providing **quantitative** results to aid in a more accurate diagnosis.

Your pathologist will find that it is simple, accurate, convenient, and reproducible. The assay can be performed on standard laboratory equipment in minutes.

Let us prove that you receive quantitative results while not disrupting the pathologist's laboratory routine. You or your pathologist should ask your Lancer representative for a demonstration or write Dept. W.O. 1831 Olive Street, St. Louis, Mo. 63103

For a direct, graphic comparison between the Lancer MB/CPK System and electrophoresis, request our brochure.

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Breda, The Netherlands

BC BRUNSWICK

Volume Studies in Men With Mild to Moderate Hypertension

JOHN H. BAUER, MD
CHARLES S. BROOKS, MD

Columbia, Missouri

The importance of salt and water in the pathophysiology of the hypertensive state is well recognized. The current study is the first to report simultaneous measurements of red blood cell mass, plasma volume, extracellular fluid and total body water levels. Studies were performed in 82 white men, 14 with normal blood pressure and 16 with low renin and 52 with normal renin hypertension. The results indicate that subjects with normal renin hypertension compared with age-matched controls are characterized by an absolute increase (1.5 liter/m^2) in intracellular fluid (total body water minus extracellular fluid). Furthermore, the ratio of extracellular fluid to total body water is decreased (0.43 to 0.38). No volume differences were found between subjects with low renin hypertension and age-matched subjects with normal renin hypertension. We conclude that subjects with normal renin hypertension compared with age-matched peers are characterized by an expanded intracellular fluid and that subjects with low renin hypertension do not exhibit a unique volume disorder.

The importance of salt and water in the pathophysiology of the hypertensive state is well recognized. Attempts to define consistently one or more volume disorders in the renin subgroups of hypertensive human beings have been unsuccessful.[1] Our study was designed to measure simultaneously red blood cell mass, plasma volume, extracellular fluid and total body water levels in low and normal renin subgroups of hypertensive patients. Simultaneous measurements of these body fluid spaces permitted the unique evaluation of both the interstitial fluid (extracellular fluid minus plasma volume) and the intracellular fluid (total body water minus extracellular fluid).

Methods

Subjects (Table I): *Control subjects:* Fourteen normal white male volunteers with no history of hypertension, maintaining a casual outpatient systolic blood pressure of less than 140 mm Hg and a diastolic blood pressure of less than 90 mm Hg, were studied in the Clinical Research Center, University of Missouri Medical Center. They ranged in age from 24 to 34 years. All were in excellent health as defined by a normal history and physical examinations.

Subjects with normal renin hypertension: Fifty-two white hypertensive men with normal renin levels were studied on a free diet and without drug therapy for 3 weeks. To be studied, subjects had to maintain a casual outpatient systolic blood pressure greater than 140 mm Hg and a diastolic blood pressure greater than 90 mm Hg. They ranged in age from 20 to 62 years. All exhibited absence or only minor degrees of cardiac, renal or vascular impairment. Specifically excluded were persons with diabetes mellitus, peripheral vascular disease, cardiomegaly, congestive heart failure, renal insufficiency (creatinine clearance less than 60 ml/min per 1.73 m^2), proteinuria or grade 3 or 4 Keith-Wagener hypertensive retinopathy.

Normal renin hypertensive subjects were further subdivided into two groups based solely on age: (1) 16 subjects aged 20 to 35 years with normal renin hypertension age-matched with control subjects; and (2) 36 subjects aged 35 to 62

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TABLE I

Patient Characteristics*

	Control Subjects	NRH_A	$P^\dagger$	LRH	NRH_B	$P^\ddagger$
Age (yr)	26.4 ± 0.8	26.5 ± 1.2	NS	48.6 ± 2.6	48.8 ± 1.1	NS
Weight (kg)	78.9 ± 3.2	83.0 ± 2.9	NS	90.6 ± 4.9	88.2 ± 1.9	NS
Height (cm)	182.1 ± 1.8	177.1 ± 2.0	NS	180.1 ± 1.6	176.6 ± 1.4	NS
Surface area (m^2)	1.99 ± 0.05	2.01 ± 0.04	NS	2.06 ± 0.07	2.01 ± 0.03	NS
Blood pressure (mm Hg)						
Systolic	112 ± 2	130 ± 2	<0.0001	152 ± 5	146 ± 3	NS
Diastolic	68 ± 2	88 ± 2	<0.0001	102 ± 2	100 ± 2	NS
Heart rate (beats/min)	63 ± 2	77 ± 4	<0.005	70 ± 2	71 ± 1	NS
no.	14	16		16	36	

* Mean ± standard error of the mean.
† Comparison of normotensive control subjects and age-matched (younger than 35 years) subjects with normal renin hypertension (NRH_A).
‡ Comparison of subjects with low renin hypertension (LRH) and age-matched (older than 35 years) subjects with normal renin hypertension (NRH_B).
NS = not significant; *P* = probability.

TABLE II

Patient Protocol

Time (hours)	Procedure
	Day 1
1200	Admission to Clinical Research Center or Renal Ward History and physical examination Weight and height measurements Free fluids and diet
2400	Start of overnight fast
	Day 2
0800	Basal blood pressure and heart rate determination (10 measurements using a mercury sphygmomanometer). Overnight recumbent humoral and blood chemistry studies (see subsequent data).
0830	Volume studies (see text)
1200	Free fluids and diet
2400	Start of overnight fast
	Day 3
0600	Assumption of 2 hour upright posture
0800	Upright (before saline infusion) humoral and blood chemistry studies Start of absolute bed rest Start of infusion (0.9 percent) of normal saline solution (500 ml/hr)
1200	Termination of saline infusion Recumbent (after saline infusion) humoral and blood chemistry studies Free fluids and diet
2400	Start of overnight fast
	Day 4
0600	Assumption of 2 hour upright posture
0800	Upright (before furosemide administration) humoral and blood chemistry studies Start of constant diet: 10 mEq sodium, 70 mEq potassium Fluid restriction: weight (kg) × 24 ml distilled water
1000	Administration of furosemide, 40 mg orally
1400	Administration of furosemide, 40 mg orally
1800	Administration of furosemide, 40 mg orally
2400	Start of overnight fast
	Day 5
0600	Assumption of 2 hour upright posture
0800	Upright (after furosemide administration) humoral and chemistry studies High salt diet and free fluids
1200	Discharge

years with normal renin hypertension age-matched with subjects with low renin hypertension.

Subjects with low renin hypertension: Sixteen white men with low renin hypertension meeting the identical criteria enumerated for men with normal renin hypertension were similarly studied. These subjects ranged in age from 47 to 57 years except for two men aged 19 and 29.

Informed consent was obtained according to the principles of the Declaration of Helsinki. All studies were approved by the Harry S. Truman Memorial Veterans Hospital and the University of Missouri Joint Committee for Research Involving Human Subjects.

Patient protocol: Control and hypertensive subjects were studied according to the protocol outlined in Table II.

Volume studies: Simultaneous volume studies were performed as previously described.[2] Radionuclides and average dosages employed were: red cell mass: ^{51}chromium-tagged red blood cells, 10 μCi; plasma volume: ^{125}iodinated human serum albumin, 5 μCi; extracellular fluid: sodium^{35} sulfate, 75 μCi; total body water: tritiated water, 90 μCi. The cumulative radiation exposure was estimated to be less than 100 mrads.

Humoral studies: Plasma renin activity assay: Venous blood was collected in chilled ethylenediaminetetraacetic acid (EDTA)-containing test tubes and spun in a refrigerated centrifuge to separate plasma. The pH of 1 ml of plasma was adjusted to approximately 5.5 with the addition of 0.38 M citric acid. Approximately 7 μg diisopropyl fluorophosphate (DFP) was added to each sample to inhibit converting enzymes. All samples were incubated at 37° C for 30 minutes. Then 10 μl of each sample was assayed according to a previously described radioimmunoassay for generated angiotensin I.[3]

Plasma aldosterone assay: Venous blood was collected in chilled heparin-containing test tubes and spun in a refrigerated centrifuge to separate plasma. Plasma samples of 1 ml were extracted with 11 ml methylene chloride with 3 drops sodium hydroxide and 0.1 molar hydrochloric acid and subsequently rinsed with distilled water. Samples were dried under nitrogen (N_2) and the extract placed on a 60 by 1 cm glass column prepared with Sephadex® LH-20M dichloromethene:methanol (98:2). The 60 to 72 ml fraction containing the aldosterone was eluted, dried under nitrogen (N_2) and reconstituted with 200 μl of ethanol. Then 50 μl of the reconstituted sample was assayed according to a previously described radioimmunoassay for aldosterone.[4]

TABLE III

Renin-Aldosterone Profiling*

	Control Subjects	NRH_A	P†	LRH	NRH_B	P‡
PRA (ng/ml per hr)						
Recumbent	1.4 ± 0.4	1.2 ± 0.1	NS	1.0 ± 0.1	1.0 ± 0.1	NS
Before infusion saline	5.1 ± 0.7	6.7 ± 1.6	NS	1.0 ± 0.1	5.2 ± 0.9	<0.0001
After infusion saline	0.9 ± 0.1	1.0 ± 0.1	NS	0.8 ± 0.1	0.9 ± 0.1	NS
Before furosemide	3.1 ± 0.6	3.8 ± 0.9	NS	0.8 ± 0.1	2.5 ± 0.4	<0.001
After furosemide	25.5 ± 3.7	19.9 ± 2.3	NS	1.7 ± 0.2	13.3 ± 1.7	<0.001
PA (ng/dl)						
Recumbent	9.0 ± 0.9	14.3 ± 4.9	NS	11.1 ± 1.6	6.9 ± 0.6	NS
Before infusion saline	27.8 ± 4.2	42.1 ± 4.9	<0.02	27.9 ± 3.1	33.0 ± 2.8	NS
After infusion saline	3.8 ± 0.5	4.3 ± 0.8	NS	3.1 ± 0.4	3.7 ± 0.4	NS
Before furosemide	16.3 ± 1.7	18.8 ± 2.4	NS	14.8 ± 2.3	13.9 ± 2.0	NS
After furosemide	65.9 ± 7.9	50.5 ± 5.1	NS	28.7 ± 4.0	34.7 ± 3.4	NS
no.	14	16		16	36	

* Mean ± standard error of the mean.
† Comparison of normotensive control subjects and age-matched subjects with normal renin hypertension (NRH_A).
‡ Comparison of subjects with low renin hypertension (LRH) and age-matched subjects with normal renin hypertension (NRH_B).
NS = not significant; P = probability; PA = plasma aldosterone, expressed as ng/dl; PRA = plasma renin activity, expressed as ng/ml per hour.

Renin-aldosterone profiling: A 3 day protocol, adapted from Grim et al.,[5] was used to evaluate the dynamic responses of the renin-aldosterone system. In our laboratory, low renin hypertension is defined as the failure of plasma renin activity to stimulate greater than 4.0 ng/ml per hr after the low sodium diet, 120 mg furosemide and an upright posture (corresponds to postfurosemide plasma renin activity). Our normal mean ± the standard deviation is 26.7 ± 13.8 ng/ml per hr, with a range of 4.7 to 56.7 ng/ml per hr. High renin hypertension is defined as the failure of plasma renin activity to suppress less than 2.0 ng/ml per hr after saline infusion and a recumbent posture (corresponds to postsaline plasma renin activity). Our normal mean ± the standard deviation is 0.9 ± 0.3 ng/ml per hour, with a range of 0.5 to 1.9 ng/ml per hour. Subjects with primary aldosteronism are distinguished from those with low renin hypertension by the latter's suppression of plasma aldosterone to less than 8.0 ng/dl after saline infusion and a recumbent posture (corresponds to postsaline plasma aldosterone). Our normal mean ± the standard deviation is 3.8 ± 1.8 ng/dl, with a range of 0.2 to 7.4 ng/dl. The foregoing data from our laboratory compare favorably with those of Grim et al.[5] This method of profiling subjects into renin subgroups has been recommended as a sensitive and reproducible method for identifying distinct homogeneous groups of patients with essential hypertension.[6]

Chemical analysis: Sodium, potassium, chloride, glucose, urea nitrogen and creatinine concentrations in serum were measured by autoanalyzer techniques using the Autoanalyzer II (Technicon Instruments, Tarrytown, New York). Serum total carbon dioxide was determined by a pH blood gas analyzer and acid base calculator (Instrument Laboratories 513).

Statistics: Nonparametric statistics were employed because the data were not necessarily normally distributed. The Wilcoxon rank sum test (Mann-Whitney test) was used to compare independent groups.[7] Significant levels were selected as $P < 0.05$. Linear (least squares) regressions were constructed and correlation coefficients determined to relate body fluid spaces to surface area, body weight, height, blood pressure and plasma renin activity using a Hewlett-Packard 9810 desk top computer.

For statistical analysis, normotensive control subjects were compared with age-matched hypertensive subjects having similar body composition, renin-aldosterone profiling and serum chemistry profiling. Additionally, subjects with low renin hypertension were compared with age-matched subjects with normal renin hypertension having similar body composition and chemistry profiling.

Results

Basal blood pressure-heart rate determination (Table I): Overnight recumbent (basal) systolic and diastolic blood pressures were elevated in subjects with normal renin hypertension (of both age groups) and in subjects with low renin hypertension compared with control subjects. Although the mean basal diastolic blood pressure in subjects with normal renin hypertension younger than age 35 was 88 mm Hg, all of these subjects had a casual diastolic blood pressure greater than 90 mm Hg. Such a disparity between basal and casual blood pressure determination has commonly been observed.[8] Subjects with normal renin hypertension older than age 35 had significantly ($P < 0.05$) higher systolic and diastolic blood pressures than subjects with normal renin younger than age 35 years. There were no blood pressure differences between age-matched hypertensive subjects with low renin and normal renin.

Overnight recumbent heart rate was elevated in the hypertensive subjects with normal and low renin compared with the control subjects. There were no significant heart rate differences between the hypertensive subgroups.

Renin-aldosterone profiling (Table III): No differences between control subjects and age-matched subjects with normal renin hypertension were found in the plasma renin activity determinations. The presaline plasma aldosterone level was higher in age-matched subjects with normal renin hypertension than in control subjects; no other differences in plasma aldosterone were observed. The only significant ($P < 0.01$) differences between subjects with normal renin younger and older than age 35 years were in postfurosemide plasma renin activity and plasma aldosterone.

TABLE IV

Serum Chemistry Profile*

	Control Subjects	NRH_A	$P^\dagger$	LRH	NRH_B	$P^\ddagger$
Glucose (mg/dl)	91.7 ± 2.2	87.1 ± 1.6	NS	98.9 ± 3.9	102.7 ± 2.6	NS
Urea nitrogen (mg/dl)	16.2 ± 0.5	14.4 ± 1.2	NS	15.1 ± 0.9	14.8 ± 0.6	NS
Creatinine (mg/dl)	1.1 ± 0.1	1.2 ± 0.1	NS	1.3 ± 0.1	1.2 ± 0.1	NS
Sodium (mEq/liter)	144.3 ± 0.7	141.2 ± 0.6	NS	142.1 ± 0.8	140.7 ± 0.8	NS
Potassium (mEq/liter)	4.4 ± 0.1	4.2 ± 0.1	NS	4.2 ± 0.1	4.1 ± 0.1	NS
Chloride (mEq/liter)	103.9 ± 0.5	102.4 ± 0.5	NS	103.5 ± 0.6	103.3 ± 0.5	NS
Total CO_2 (mEq/liter)	27.8 ± 0.4	27.7 ± 0.5	NS	27.1 ± 0.9	27.7 ± 0.4	NS
no.	14	16		16	36	

* Mean (mg/dl or mEq/liter) ± standard error of the mean.
† Comparison of normotensive control subjects and age-matched subjects with normal renin hypertension (NRH_A).
‡ Comparison of subjects with low renin hypertension (LRH) and age-matched subjects with normal renin hypertension (NRH_B).
NS = not significant; P = probability.

As anticipated, subjects with low renin hypertension differed from age-matched subjects with normal renin in the presaline-, prefurosemide- and postfurosemide-stimulated plasma renin activity determinations. There were no differences in the plasma aldosterone determinations between age-matched hypertensive subjects with low and normal renin levels.

Serum chemistry profile (Table IV): There were no differences in the serum chemistry determinations between control subjects and age-matched subjects with normal renin hypertension or between low renin and age-matched normal renin hypertensive subjects.

Volume characteristics (Table V): There were no differences in red blood cell mass, plasma volume and total blood volume between control subjects and age-matched normal renin hypertensive subjects. Large vessel (venous) hematocrit, whole body hematocrit and the ratio of whole body to large vessel hematocrit were not different. No differences in extracellular fluid, interstitial fluid or total body water were observed. The intracellular fluid, however, was greater (1.5 liter/m^2) in subjects with normal renin hypertension than in age-matched control subjects. There were no differences in the ratios of plasma volume to extracellular fluid or total body water between control subjects and age-matched subjects with normal renin hypertension. There was a downward alteration (from 0.43 to 0.38) in the ratio of extracellular fluid to total body water in subjects with normal renin hypertension compared with age-matched control subjects.

There were no differences in red blood cell mass, plasma volume and total blood volume between age-matched hypertensive subjects with low and normal renin levels. Values for large vessel hematocrit, whole body hematocrit and the ratio of whole body to large vessel hematocrit were not different. Extracellular fluid, total body water, interstitial fluid and intracellular fluid were not different in age-matched subjects with low and normal renin hypertension. The intracellular fluid was significantly ($P < 0.02$) greater in hypertensive subjects with low and normal renin levels older than age 35 years compared with control subjects, but values were not different from those in subjects with normal renin hypertension younger than age 35. There were no differences in the volume ratios between age-matched hypertensive subjects with low and normal renin levels.

Correlation studies: These were performed for each body fluid space (liter/m^2) and both systolic and diastolic basal blood pressure in age-matched subjects. The only significant correlation found was that for intracellular fluid and diastolic blood pressure ($r = 0.3797$, $P < 0.05$).

Correlation studies were performed for each body fluid space and plasma renin activity in age-matched subjects and in the combined groups of hypertensive subjects. No significant correlations were found.

To establish the importance of body surface area, body weight and height in the analysis of volume indexes, correlation studies were performed for each body fluid space (expressed as liters), and surface area, body weight and height in the combined groups of hypertensive subjects. Significant positive correlations were found between each volume measured and body surface area, body weight and height. However, when volume indexes were expressed as a function of surface area (liter/m^2), the significance of these correlations was lost.

Discussion

Our study is the first to report simultaneous determinations of red blood cell mass, plasma volume, extracellular fluid and total body water levels in well defined homogeneous renin subgroups of hypertensive subjects. In comparing volume indexes between groups, all mean volume data were expressed as either liter/m^2 or as a ratio of one absolute space to another (in liters) to negate the potential influence of weight and height on its determination.

Control Subjects Versus Age-Matched Subjects With Normal Renin Hypertension

Our results demonstrate that subjects with normal renin hypertension compared with age-matched control subjects have similar body fluid characteristics. They differ only in that the hypertensive subjects have an increase in the intracellular fluid. Furthermore, the ratio

TABLE V

Volume Characteristics*

	Control Subjects	NRH_A	$P^\dagger$	LRH	NRH_B	$P^\ddagger$
RCM	1.06 ± 0.04	1.02 ± 0.03	NS	1.04 ± 0.03	1.05 ± 0.02	NS
PV	1.66 ± 0.05	1.56 ± 0.03	NS	1.68 ± 0.05	1.60 ± 0.02	NS
TBV	2.72 ± 0.08	2.58 ± 0.05	NS	2.73 ± 0.06	2.65 ± 0.04	NS
ECF	9.0 ± 0.3	8.6 ± 0.3	NS	8.5 ± 0.3	8.3 ± 0.2	NS
TBW	21.2 ± 0.7	22.3 ± 0.4	NS	22.2 ± 0.4	22.4 ± 0.3	NS
ISF	7.8 ± 0.5	7.0 ± 0.3	NS	6.9 ± 0.3	6.9 ± 0.2	NS
ICF	12.3 ± 0.7	13.8 ± 0.4	<0.025	13.6 ± 0.5	14.2 ± 0.4	NS
HCT_v	0.46 ± 0.01	0.46 ± 0.01	NS	0.46 ± 0.01	0.47 ± 0.01	NS
HCT_0	0.39 ± 0.01	0.39 ± 0.01	NS	0.38 ± 0.01	0.40 ± 0.01	NS
F cell	0.84 ± 0.01	0.85 ± 0.01	NS	0.83 ± 0.01	0.84 ± 0.01	NS
PV/ECF	0.19 ± 0.01	0.18 ± 0.01	NS	0.20 ± 0.01	0.20 ± 0.01	NS
PV/TBW	0.08 ± 0.01	0.07 ± 0.01	NS	0.08 ± 0.01	0.07 ± 0.01	NS
ECF/TBW	0.43 ± 0.01	0.38 ± 0.01	<0.01	0.39 ± 0.02	0.37 ± 0.01	NS
no.	14	16		36	16	

* Mean (liter/m^2) ± standard error of the mean.
† Comparison of normotensive control subjects and age-matched subjects with normal renin hypertension (NRH_A).
‡ Comparison of subjects with low renin hypertension (LRH) and age-matched subjects with normal renin hypertension (NRH_B).
ECF = extracellular fluid; F cell = HCT_0/HCT_v; HCT_0 = whole body hematocrit; HCT_v = large vessel hematocrit; ICF = intracellular fluid (TBW − ECF); ISF = interstitial fluid (ECF − PV); NS = not significant; *P* = probability; PV = plasma volume; RCM = red cell mass; TBV = total blood volume (RCM + PV); TBW = total body water.

of extracellular fluid to total body water is significantly depressed. This depression may be caused by either a redistribution of salt and water from the extracellular fluid into the intracellular fluid or to an excess accumulation of salt and water in the intracellular fluid. The only volume-pressure correlation found was that between the intracellular fluid and basal diastolic blood pressure.

Our inability to demonstrate a significant decrease in extracellular fluid may reflect either the absence of a true difference between the extracellular fluid of subjects with normal renin hypertension and that of control subjects, as suggested by others,[9–13] or an insufficient number of subjects studied to define a 0.4 liter/m^2 difference between groups. Our inability to demonstrate a significant increase in total body water may be due to either the offsetting effect of a mean decrease in extracellular fluid or the insufficient numbers of subjects studied to define a 1.1 liter/m^2 difference.

The increased content of water (waterlogging) in the vascular smooth muscle has been suggested by several investigators as an important factor in the pathogenesis of essential hypertension.[14–16] The salt and water composition of arterial walls is abnormal in many forms of hypertension, including human essential hypertension.[14,15] In hypertension, abnormal water and ionic contents have occurred in many other tissues in addition to arteries, including veins,[17] myocardium,[18] skeletal muscle,[14,18] submaxillary gland,[19] brain,[14,18] and liver, gut, spleen and skin.[18] In conjunction with this factor, our findings of an expanded intracellular fluid level, a depressed extracellular fluid to total body water ratio and a positive correlation between the intracellular fluid and diastolic blood pressure suggest that the mildly hypertensive state may be characterized by an underlying defect in cell ion metabolism.

Our results did not demonstrate a difference in red blood cell mass, plasma volume, total blood volume or whole body or large vessel hematocrit between control subjects and age-matched subjects with normal renin hypertension. Whole body hematocrit denotes the average distribution of red cells in the plasma throughout the vascular system and is accurately determined by measuring these two components of blood separately with appropriate tracers.[20,21] Such measurements have shown that the venous hematocrit is not representative of the proportion of red cells found in the total blood volume. The discrepancy is expressed as the ratio of whole body hematocrit to large vessel hematocrit, and is termed the F cell ratio.[20,21] It has been suggested that conditions favoring a reduction in the cross-sectional diameter of the vascular bed would be associated with a reduced F cell ratio.[21] However, we found no evidence, that the F cell ratio was different in the subjects normal renin hypertension and control subjects.

Plasma volume: This value has variously been reported to be normal or decreased in hypertensive subjects not receiving drug therapy (Table VI). Such inconsistent findings probably reflect the variations in: (1) sex and race of the subject, (2) blood pressure, (3) diet, (4) technique employed (10 to 60 minutes of equilibration sampling of various types of tracers), and (5) expression of data (ml/kg, liter/m^2, ml/cm). Comparative evaluations should be made only if the subject populations are similar in sex and race, have similar degrees of hypertension and end-organ damage and have been placed on similar dietary programs. The technique employed to measure plasma volume must ensure complete distribution and mixing of the tracers; sampling blood between 30 and 60 minutes assures this requirement.[21] Finally, because there is a direct correlation between plasma volume (expressed as liters) and body weight ($r = 0.7346$, $P < 0.001$) and height ($r = 0.5622$, $P < 0.001$), reference to both indexes should be included in the expression of plasma volume; reference to surface area appears to resolve this problem.

TABLE VI

Published Results on Plasma Volume (ml/kg or liter/m^2) in Hypertensive Subjects

Series	Control Subjects		Hypertensive Subjects		Significance (P)		Sex	Race	Diastolic Blood Pressure Range	Diet
	ml/kg	liter/m^2	ml/kg	liter/m^2	ml/kg	liter/m^2				
Teng et al.[37]	...	1.73	...	1.81	...	NS	M+F	‖	≥100	‖
Tibblin et al.[38]	47.3	...	39.6	...	<0.005	...	M	‖	≥110	‖
Tarazi et al.[22]	47.9	1.95	42.3	1.82	<0.001	<0.02	M	‖	‖	Free
Julius et al.[28]	44.7	...	37.2	...	<0.001	...	M	‖	Borderline	‖
Brown et al.[26]	38.8	...	34.1	...	NS	...	M	W+B	‖	250 mEq/day
Ibsen and Leth[11]	...	1.89*	...	1.68*	...	<0.001*	M/F	‖	‖	‖
		1.62†		1.55†		NS†				
Safer et al.[39]	43.1	...	41.3‡	...	NS‡	...	M+F	‖	Borderline	‖
			39.0§		<0.001§					
Parving and Gyntelberg[40]	48.3	1.88	41.4	1.66	<0.01	<0.005	M	‖	≥100	‖
Tarazi[41]	...	1.65	...	1.48	...	<0.001	M	‖	‖	Free
Bauer and Brooks (present study)	...	1.66	...	1.56	...	NS	M	W	≥90	Free

* Male.
† Female.
‡ Normal cardiac output.
§ Exhibiting high cardiac output.
‖ Data not provided.
B = black; NS = not significant; P = probability; W = white.

If the foregoing requirements are considered, our results may best be compared with the findings of Tarazi et al.[22] and Ibsen and Leth.[11] In the former series, a significant reduction in plasma volume appeared to begin in hypertensive patients whose diastolic pressures exceeded 105 mm Hg, and in the latter series the mean diastolic pressure was 119 mm Hg. In our series, basal diastolic pressure was less than 105 mm Hg in all but one subject with normal renin hypertension younger than age 35. We are therefore defining the absence of an abnormal pressure-volume relation in subjects with mild hypertension. These results appear to agree with the observations of Tarazi et al.[22]

Total blood volume, expressed as a function of surface area and determined by dual tracers, has previously been reported only by Hansen.[23] He reported no significant difference in total blood volume between normotensive and hypertensive women. Although our study was restricted to white men, it supports the observation of Hansen in that we found no significant difference in either total blood volume or any of its components between control subjects and age-matched subjects with normal renin hypertension. Although others have variously reported total blood volume to be normal[24–29] or decreased[30] in hypertensive subjects compared with normotensive subjects, their data were derived from only one tracer plus hematocrit, and they either did not separate sex or did not express their results as a function of surface area.

The finding of a reduced plasma volume and normal extracellular fluid volume by Tarazi et al.,[10] and Ibsen and Leth[11] suggested to them a disturbance in the partition between the intracellular and interstitial compartments of the extracellular fluid. Our data, derived from studying subjects with milder hypertension, do not demonstrate a disturbance in the forces regulating extracellular fluid partition. The difference in results may be explained by (1) the variation in severity of hypertension, and (2) the use of sulfate space versus bromide space to measure extracellular fluid.

Blood volume versus diastolic blood pressure and plasma renin activity: Tarazi et al.[22] and Julius et al.[28] reported a significant inverse relation between plasma volume (expressed as ml/cm or ml/kg) and diastolic blood pressure. However, in a more recent work, Tarazi et al.[31] demonstrated this correlation only if eight patients with an "inappropriate plasma volume expansion" were excluded from a series consisting of 55 hypertensive men. Furthermore, Ibsen and Leth[11] could not verify this relation when expressing plasma volume as a function of surface area. Our data tend to support those of Ibsen and Leth[11]; we found no correlation between plasma volume or total blood volume and either systolic or diastolic basal blood pressure. Dustan et al.[32] reported that plasma volume is inversely correlated with plasma renin activity in men with essential hypertension. Because our study was designed to compare normotensive and hypertensive subjects having similar renin profiling, it was expected, and found, that there was no correlation between plasma renin activity and plasma volume or any other body fluid space measured.

Low Renin Hypertension Versus Normal Renin Hypertension in Age Matched Subjects

Our results demonstrate that subjects with normal renin hypertension have serum chemistry profiling and body fluid characteristics similar to those of subjects with low renin hypertensive subjects matched for age, body composition and degree of hypertension. Schalekamp et al.[33] reported no difference in either plasma volume or extracellular fluid (expressed as liter/m^2) between normotensive control subjects and subjects with either normal or low renin hypertension. However,

their study was performed in subjects consuming a low sodium diet (50 mEq/day). Jose et al.[34] found a higher extracellular fluid volume (expressed as liter/m^2) in five black women with low renin hypertension than in seven black men and women having normal renin hypertension while consuming a regular diet (200 mEq/day); however, plasma volume was not different between the groups. Woods et al.[35] found no difference in plasma volume (expressed as ml/kg) between men and women with normal and low renin hypertension, although exchangeable sodium was higher in hypertensive subjects with low renin than in those with normal renin. Conversely, Lebel et al.[36] found no difference in exchangeable sodium between normotensive men and women and hypertensive subjects with either low or normal renin hypertension.

Implications: Our data clearly demonstrate no difference in any body fluid space or in any body fluid ratio between age-matched white men with low and normal renin hypertension. These findings suggest that subjects with low renin hypertension cannot be identified from subjects with normal renin hypertension by a unique volume disorder and that the suppressed renin state is probably unrelated to volume excess.

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Surgery for Life-Threatening Ventricular Tachyarrhythmias

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Among 203 left ventricular aneurysmectomies performed since 1970, the operative mortality rate was 18.7 percent. In 49 patients (24 percent), left ventricular aneurysmectomy was performed for refractory life-threatening ventricular arrhythmias. Eight additional patients had coronary bypass grafting without ventricular aneurysmectomy. One of these patients had bypass grafting followed later by ventricular aneurysmectomy. All 56 patients had underlying coronary artery disease. The operative mortality rate was 19.6 percent. In patients with a recent myocardial infarction, the rate was 60 percent, whereas it was 11 percent in patients with a remote myocardial infarction. Other high risk variables in these patients included coronary bypass grafting without myocardial resection, and an elevated left ventricular end-diastolic pressure. The late mortality rate was 17.9 percent, but only one of these deaths was sudden and unexpected. The 35 long-term survivors have been followed up for a mean of 40.7 months (range 7 to 92 months). Of these, 20 remain on antiarrhythmic medications for palpitation or documented ventricular premature complexes, whereas 15 are free of detectable rhythm disturbances and do not require antiarrhythmic agents. Only 4 of 35 (11 percent) have had recurrent documented ventricular tachycardia. Left ventricular aneurysmectomy may be performed for refractory ventricular tachyarrhythmias with an acceptable operative mortality, particularly if the patient has survived longer than 6 weeks after myocardial infarction. Although epicardial mapping techniques may be useful in localizing the reentrant pathway of the ventricular tachycardia, ventricular aneurysmectomy without mapping techniques produces a satisfactory clinical result in the vast majority of long-term survivors.

Although ventricular aneurysm has long been recognized as a complication of myocardial infarction,[1] the initial clinical association of ventricular aneurysm with recurrent ventricular arrhythmias was made by Parkinson et al.[2] in 1938. This observation was subsequently confirmed, and the frequency of ventricular aneurysm in myocardial infarction was appreciated.[3,4] It was noted that patients with aneurysm occasionally responded poorly to drug treatment of arrhythmias, and in 1956, Couch[5] first described excision of the aneurysm as treatment for recurrent tachyarrhythmias. More recently, other surgical procedures, including combined ventricular aneurysmectomy and coronary arterial bypass grafting,[6–10] coronary bypass grafting alone[11–14] and infarctectomy,[15–17] have been performed in patients with coronary artery disease who have uncontrolled ventricular arrhythmias.

Increasing evidence supports reentry as the underlying mechanism in the genesis of recurrent ventricular tachycardia in the ischemic tissue of myocardial infarcts.[18,19] Although these observations would explain the reasons for surgery in the interruption of such pathways soon after infarction, they leave questions about the value of resection of aneu-

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rysmal tissue long after myocardial infarction. However, recent studies in man[20] utilizing programmed stimulation to induce arrhythmias suggest that reentry may also be the underlying mechanism for these arrhythmias in patients with chronic ventricular aneurysm who have recurrent life-threatening ventricular tachycardia. With the introduction of epicardial mapping techniques, the role of epicardial and endocardial mapping at the time of operation, to define sites where arrhythmias are initiated, has been argued.[21–28] Many of these techniques have been developed in canine models[21,28] or by utilizing a catheter technique for endocardial mapping.[27] These studies provide supportive evidence for endocardial and epicardial mapping at operation or in the electrophysiology laboratory. During the past decade, we have managed many patients with resistant ventricular arrhythmias and we report our extensive experience in those patients with ventricular tachyarrhythmias who were managed surgically, without epicardial mapping techniques.

Methods

Selection of patients: All patients undergoing surgical therapy for ventricular arrhythmia between January 1970 and April 1978 were identified from our computer data base. There were 56 such patients whose cases were reviewed for clinical postoperative status, hemodynamic and angiographic measurements and surgical procedures performed. The accumulated electrocardiographic and electrophysiologic data were reviewed to verify the occurrence of preoperative recurrent ventricular tachyarrhythmias and to identify the type of initiating factors. Most of these patients did not undergo sophisticated electrophysiologic studies to define precisely that the arrhythmias were of ventricular origin, although the clinical course of the patients strongly supported this concept. Patients now being subjected to surgery in our institution undergo invasive electrophysiologic studies with induction of arrhythmias. A ventricular aneurysm was defined as a discrete area of akinetic or dyskinetic myocardium determined from careful angiographic study. Coronary arterial lesions were considered to be significant if greater than 70 percent of the lumen was obstructed. A full battery of hemodynamic studies was also performed.

Preoperative drug therapy: All 56 patients were documented to have life-threatening ventricular tachycardia or fibrillation, or both. "Life-threatening" was defined as sustained arrhythmia resulting in decreased hemodynamic function. Although not all patients had syncope, the histories of acute onset of arrhythmia in the hospital setting probably accounted for this finding. Many had required heroic resuscitations[26] and were referred for study and surgical consideration. To be considered a surgical candidate, a patient must have failed to respond to at least one antiarrhythmic agent given in large enough doses to produce "high" therapeutic blood levels. Thirty-six patients were transferred from other hospitals. All of these patients were receiving antiarrhythmic agents at the time of transfer, usually lidocaine or procainamide or both. Whenever possible, administration of drugs was discontinued to permit an empiric trial of other agents. During the past 4 years, we have used plasma concentration of drugs to document that adequate drug had been administered (plasma concentrations of lidocaine greater than 5 μg/ml, of procainamide greater than 15 μg/ml and of quinidine greater than 5 μ/ml were considered high therapeutic levels). Before drug level monitoring was begun, all patients were given loading doses of the selected drug, followed by standard programs of administration. Whenever possible, the drug was given on a trial basis for 48 hours to determine whether it prevented recurrent ventricular tachycardia or fibrillation. Fifty-three of 56 patients underwent treatment with combinations of two or more agents.

Follow-up study: The patients were followed up with routine office visits and telephone interview with both the patient and his physician. In 15 patients, ambulatory arrhythmia monitoring was performed at intervals after aneurysmectomy. If a patient died, the cause of death was assessed from the autopsy report or death certificate. Clinical status, antiarrhythmic regimen and documented arrhythmias were reviewed in all surviving patients.

Results

Since 1970, a total of 203 patients underwent left ventricular aneurysmectomy at our institution for angina, congestive heart failure, ventricular tachyarrhythmias or a combination of these indications. The operative mortality of this entire group was 18.7 percent (38 of 203).

TABLE I

Clinical Data of 56 Patients

	Patients	
	no.	%
Male/female*	47/9	84/16
Coronary artery disease	56	100
Presenting symptom		
Syncope	24	43
Presyncope	10	18
Palpitation	13	23
Dyspnea	7	13
Angina	2	3
Documented arrhythmia (preoperatively)		
Ventricular tachycardia-ventricular fibrillation	26	46
Ventricular tachycardia	30	54
Antiarrhythmic drugs preoperatively		
4 or more	20	36
3	19	34
2	14	25
1	3	5

* Mean age (range) 55.4 years (33 to 79).

TABLE II

Hemodynamic and Angiographic Data

	Patients	
	no.	%
Left ventricular end-diastolic pressure (mm Hg)		
<15	15	34
≤15	29	66
Coronary artery disease* (70 percent or greater narrowing)		
1 vessel	12	22
2 vessel	15	28
3 vessel†	27	50
Left ventricular aneurysm		
Anteroapical	41‡	72
Inferoposterior	8	14
Anteroapical + inferoposterior	3	5
Hypokinesia/akinesia	5‡	9

* Two patients had surgery without coronary angiography.
† One patient had 50 percent stenotic lesions only.
‡ One patient had anterior akinesia that progressed to anteroapical aneurysm.

Of the 203 patients, 49 (24 percent) underwent left ventricular aneurysmectomy primarily for refractory, life-threatening ventricular tachyarrhythmias. Eight additional patients had coronary arterial bypass grafting without myocardial resection for ventricular tachyarrhythmias. One patient had coronary bypass grafting initially and left ventricular aneurysmectomy 29 months later and was thus included in both surgical groups. Therefore, a total of 56 patients were included in our study.

Clinical data (Table I): There were 47 men and 9 women whose mean age was 55.4 years (range 33 to 79 years). All patients had underlying coronary artery disease.

The presenting symptom was syncope in 24 patients, presyncope in 10, palpitation in 13, dyspnea in 7 and angina in 2. Twenty patients (36 percent) had evidence of congestive heart failure, and 22 patients (40 percent) had angina pectoris, but left ventricular aneurysmectomy in all patients was performed primarily for life-threatening, drug-resistant ventricular tachyarrhythmias. Two patients were in New York Heart Association[29] functional class I, 9 patients in class I, 38 patients in class III, and 6 patients in class IV.

All patients had documented ventricular tachyarrhythmias; 26 patients (46 percent) had recurrent and sustained ventricular tachycardia and ventricular fibrillation, and 30 patients (54 percent) had recurrent and sustained ventricular tachycardia alone. Ventricular tachycardia was defined as sustained if it had persisted long enough to produce deterioration of cardiac function, and as recurrent if there had been three or more episodes.

In all patients medical treatment had failed to control the arrhythmias. No patient had responded to intravenous lidocaine. Before surgical intervention, 3 patients had been treated with lidocaine alone, 14 had been treated with two antiarrhythmic drugs, 19 with three antiarrhythmic drugs and 20 with at least four antiarrhythmic drugs.

Hemodynamic and angiographic data (Table II): Forty-four patients underwent hemodynamic assessment at the time of left ventriculography and coronary angiography. Left ventricular end-diastolic pressure was less than 15 mm Hg in 15 patients (34 percent), and elevated to 15 mm Hg or greater in 29 patients (66 percent).

Fifty-four patients underwent left ventriculography and coronary angiography. Two patients, whose clinical status was deteriorating rapidly, were operated on as a surgical emergency, without prior invasive investigation. Both of these patients were found to have coronary artery disease at the time of operation. Of the patients who underwent coronary angiography, 12 had one vessel disease, 15 had two vessel disease and 27 had three vessel disease. All but one of these patients had lesions in the coronary arteries measuring at least 70 percent of the coronary arterial lumen. One patient had three vessel disease but no lesions greater than 50 percent of the coronary lumen.

The location of the left ventricular aneurysm or akinetic wall segment was determined with left ventricular angiography in 54 patients, and at operation in the 2 patients who underwent emergency operation. The subsequent location was confirmed at operation in all patients. The site of the left ventricular aneurysm was anteroapical in 41, inferoposterior in 8 and both anteroapical and inferoposterior in 3. Five patients did not have an aneurysm but did have either marked segmental hypokinesia or akinesia. One of these patients underwent a second investigation prior to a second surgical procedure and the area of anterior akinesia had progressed to an anteroapical aneurysm.

Surgical data and operative mortality (Table III): Because 1 patient had a second surgical procedure 29 months after the first, a total of 57 surgical procedures were performed in the 56 patients. Sixteen patients underwent left ventricular aneurysmectomy, 33 underwent combined left ventricular aneurysmectomy and coronary bypass grafting and 8 underwent coronary bypass grafting alone. The one patient who underwent two surgical procedures had coronary bypass grafting initially, followed later by left ventricular aneurysmectomy and coronary bypass grafting.

The interval from myocardial infarction to surgery was recorded in all patients. Forty-six patients had the operative procedure 6 weeks or more after the myocardial infarction (mean 36 months), whereas 10 patients underwent operation within 6 weeks of myocardial infarction (mean 3.7 weeks).

The operative mortality rate was 19.6 percent (11 of 56) (Table IV). Seven patients (64 percent) died as a result of recurrent ventricular arrhythmia and four (36 percent) as a result of myocardial failure. Factors re-

TABLE III

Surgical Procedures

	Patients	
	no.	%
Left ventricular aneurysmectomy	16	28
Left ventricular aneurysmectomy + coronary bypass grafting	33*	58
Coronary bypass grafting	8*	14
Time from myocardial infarction to surgery		
<6 weeks	10	18
≥6 weeks	46	82

* One patient had both procedures.

TABLE IV

Causes of Mortality

	Patients	
	no.	%
Operative		
Myocardial failure	4	36
Ventricular arrhythmia	7	64
Late		
Congestive heart failure	7	70
Sepsis	2	20
Sudden, unexpected	1	10

lated to operative mortality are illustrated in Figures 1 to 3. In 10 patients who had a myocardial infarction within 6 weeks before surgery, the operative mortality rate was 60 percent, whereas it was 11 percent in the 46 patients with a remote myocardial infarction more than 6 weeks before operation (Fig. 1). This difference was statistically significant ($P < 0.05$). When the left ventricular end-diastolic pressure was 15 mm Hg or greater, the operative mortality rate was 21 percent (6 of 29), whereas there was no operative mortality among the 15 patients with left ventricular end-diastolic pressure less than 15 mm Hg (Fig. 2). This difference did not quite reach statistical significance ($P = 0.06$). Finally, the operative mortality differed according to the surgical procedure performed. In patients undergoing coronary bypass grafting without myocardial resection, the operative mortality rate was 38 percent (3 of 8), whereas it was 16 percent (8 of 49) in patients who had left ventricular aneurysmectomy with or without coronary bypass grafting (Fig. 3). Again, a trend was noted but this difference did not reach statistical significance ($P = 0.17$).

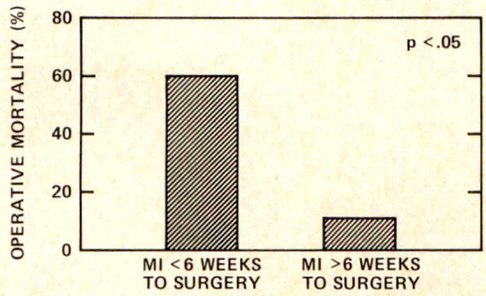

FIGURE 1. Operative mortality in 10 patients who had a myocardial infarction (MI) within 6 weeks before operation compared with that in 46 patients whose myocardial infarction more than 6 weeks before operation. p = probability.

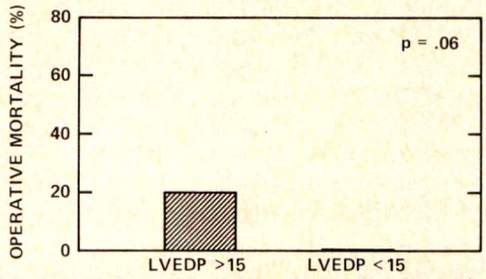

FIGURE 2. Operative mortality in 29 patients with left ventricular end-diastolic pressure (LVEDP) of 15 mm Hg or more compared with that in 15 patients whose left ventricular end-diastolic pressure was less than 15 mm Hg. p = probability.

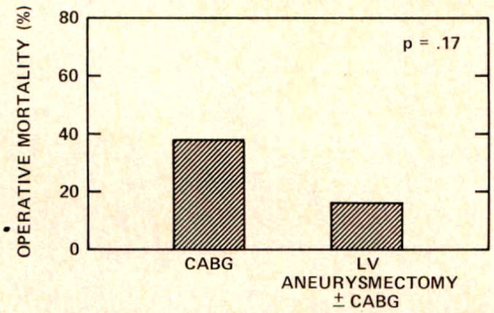

FIGURE 3. Operative mortality in 8 patients undergoing coronary bypass grafting (ABG) only compared with that in 49 patients undergoing combined left ventricular (LV) aneurysmectomy and bypass grafting. p = probability.

Late mortality: The late mortality (more than 1 month postoperatively) was 17.9 percent (10 of 56) after a mean survival of 21.7 months (range 1 to 71 months). Seven patients died as a result of congestive heart failure, two died from sepsis and one patient died suddenly and unexpectedly.

Follow-up data (Table V): The actuarial life survival curve for the entire study group is illustrated in Figure 4. In Figure 5, the actuarial life survival curves of 177 patients undergoing ventricular aneurysmectomy for various clinical indications are compared. There are 35 long-term survivors, with a mean follow-up period of 40.7 months (range 7 to 92 months). Twenty-four patients (69 percent) are asymptomatic. Eleven patients (31 percent) continue to have symptoms (syncope in two, presyncope in one, palpitation in four and angina in seven). The two patients with syncope have had ventricular premature complexes noted on Holter ambulatory monitoring without documentation of ventricular tachycardia. Both patients are now receiving antiarrhythmic medications.

Holter ambulatory monitoring was performed in 15 patients (43 percent) who continue to have symptoms or ventricular premature complexes noted in the standard 12 lead electrocardiogram. All patients had one control monitoring and at least one monitoring while receiving drug therapy. No exact protocol was followed in these studies. Recurrent ventricular tachycardia was noted in four patients (11 percent). Two of these pa-

TABLE V

Follow-Up Data in 35 Patients

	Patients	
	no.	%
Symptoms	11	31
Syncope	2	
Presyncope	1	
Palpitation	4	
Angina	7	
Holter monitoring studies	15	43
Ventricular tachycardia	4	
Frequent VPCs (>10 complexes/15 min)	7	
Occasional VPCs (<10 complexes/15 min)	4	
Antiarrhythmic medications	20	57
Propranolol	5	
Quinidine	7	
Procainamide	8	
Disopyramide	3	
Diphenylhydantoin	1	
No antiarrhythmic medication	15	43

* Mean follow-up time 40.7 months (range 7 to 92).
VPCs = ventricular premature complexes.

tients have had subsequent hospitalization for management of this problem, whereas two patients have been asymptomatic with regard to the ventricular tachycardia, and this arrhythmia was noted for 5 to 10 second periods only on Holter monitoring. Of the remaining 11 patients who underwent Holter monitoring, 7 had frequent ventricular premature complexes (more than 10 beats/15 min), whereas 4 had occasional ventricular premature complexes (fewer than 10 beats/15 min). Ventricular tachycardia was not noted in any of these patients. Clearly, Holter monitoring was performed in only symptomatic patients or those with ventricular arrhythmias detected by other means. This experience cannot be extrapolated to the entire group.

Antiarrhythmic medications have been resumed in 20 patients (57 percent), including the patients with recurrent ventricular arrhythmias. Symptoms or detection of ventricular tachycardia or frequent premature ventricular complexes (more than 40/hour) were indications for drugs. Antiarrhythmic drug therapy in these patients after operation was chosen empirically. Plasma concentrations were measured to assure compliance and achievement of adequate plasma concentrations. The antiarrhythmic medications used include propranolol in five, quinidine in seven, procainamide in eight, disopyramide in three and diphenylhydantoin in one. Fifteen patients (43 percent) are not receiving antiarrhythmic medication because no recurrent ventricular arrhythmias have been detected.

Discussion

Recurrent ventricular tachyarrhythmias are life-threatening in many patients, but in general may be controlled by rigorous application of antiarrhythmic medical therapy.[30,31] However, in a small subgroup of patients who fail to respond to medical management, more extensive electrophysiologic studies and consideration of surgical treatment are indicated. As outlined in this study, this therapy can prove to be extremely successful.

During the past 8 years at Stanford Medical Center, 24 percent of all 203 patients undergoing ventricular aneurysmectomy underwent this procedure primarily for recurrent life-threatening ventricular arrhythmias refractory to medical management as defined. Although our figures may reflect our present patient selection for aneurysm resection, they emphasize that this is a common problem in a tertiary referral center where many patients with coronary artery disease are seen. Our experience differs significantly from that of the Cleveland Clinic,[6] where only 4 percent of 400 patients undergoing operation for ventricular aneurysm underwent the procedure because of intractable arrhythmias. The operative mortality for left ventricular aneurysmectomy for other indications, usually angina or congestive heart failure, or both, was not significantly different from the operative mortality for refractory ventricular tachyarrhythmias (Fig. 5). Of the 11 operative deaths, 4 (36 percent) were due to heart failure from loss of excessive myocardium, but 7 (64 percent) were due to uncontrolled ventricular arrhythmias. Clearly, surgery was not always effective and, depending on interpretation, the 20 patients who require drug therapy plus the 7 who died of arrhythmia could be considered surgical failures. On the other hand, the 20 who required drug treatment but survived could be considered surgical successes.

Clinical features defining high surgical risk: In our study group, certain variables were identified to define the high risk surgical candidates among the patients with refractory ventricular arrhythmias. First, patients whose myocardial infarction occurred within 6 weeks before operation had an operative mortality of 60 percent, significantly higher than those whose surgical procedure was remote relative to previous myocardial infarction. This finding agrees with our previous reported experience[7,8] and that of others.[32,33]

A second high risk variable identified in this study was coronary artery bypass grafting without myocardial resection. Of the eight patients who underwent this

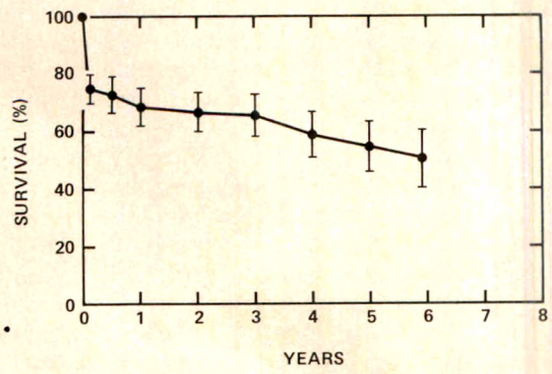

FIGURE 4. Actuarial life survival curve for all 56 patients undergoing surgery for refractory ventricular tachyarrhythmias.

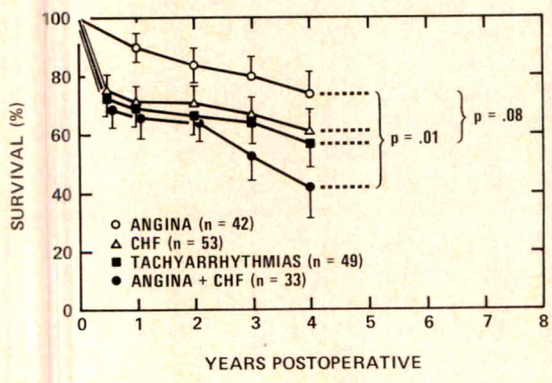

FIGURE 5. Actuarial life survival curve for 177 patients undergoing left ventricular aneurysmectomy for specific clinical indications, including angina, congestive heart failure (CHF), ventricular tachyarrhythmias and angina with congestive heart failure. The only statistically significant difference is between patients undergoing aneurysmectomy for angina and those undergoing aneurysmectomy for angina plus congestive heart failure. n = number of patients; p = probability.

surgical procedure, there were three operative deaths, and two additional patients died within 4 months of surgery. Two of the three surviving patients had had recurrent ventricular tachycardia 3 months postoperatively. One of these patients has undergone a second surgical procedure (aneurysm resection) for this problem. Although others[11–14] have reported success in suppressing ventricular arrhythmias by bypass grafting procedures without myocardial resection, it is our general opinion that these patients do poorly. The studies reporting success of coronary arterial bypass grafting alone in reducing sudden death have not used a randomized control population for comparison, and the comparability of the level of illness in the groups is questionable. Exercise-induced ventricular arrhythmias do not appear to be altered by coronary bypass surgery.[34] Many ventricular tachyarrhythmias are due to reentry, occurring because of ischemic tissue in the conduction system, and surgical interruption of the pathway may abolish the arrhythmias. Although coronary bypass surgery alone has been reported to decrease sudden cardiac death, it did not alter the occurrence of arrhythmias in our study. Our patients may represent a different subgroup with reentry pathways in the ventricular aneurysm or perianeurysmal tissue, and they do not appear to benefit from bypass alone. For this reason, we do not at this time recommend bypass grafting without myocardial resection for the treatment of documented refractory ventricular arrhythmias.

The third high risk variable relates to the patient's preoperative hemodynamic status. There were no operative deaths in patients with left ventricular end-diastolic pressures less than 15 mm Hg, in contrast to an operative mortality rate of 21 percent in the patients whose left ventricular end-diastolic pressure was 15 mm Hg or greater. This difference is a reflection of the viable myocardium remaining and the compensation which the patient has achieved.

Role of preoperative epicardial mapping: Our study was performed without using epicardial mapping to locate the activation sequence on the epicardial surface of the ventricle, and it raises some practical questions. Kastor et al.[21] demonstrated that epicardial mapping could be used to locate the origin of ventricular ectopic complexes. Their studies confirmed the concentric spread of excitation away from the inciting focus, suggesting the possibility of epicardial mapping for localization of sites of origin of ectopic impulses in the myocardium. Although it is recognized that the ectopic site of origin is probably in the subendocardial area, it was thought that identification of the point of breakthrough would identify this site. Since then, several investigators[35–39] have applied epicardial mapping techniques to the study of preexcitation syndromes and have demonstrated their usefulness at the time of surgery for life-threatening or disabling arrhythmias. Subsequently, this technique has also been successfully applied to the surgical management of patients with coronary artery disease, left ventricular aneurysm and refractory ventricular arrhythmias.[24,26,27] Although the number of patients studied to date is small, it is clear that epicardial mapping may be useful in some patients.

Our study has identified specific problem areas where epicardial mapping techniques may be useful. Because 64 percent of our operative deaths were a result of intractable or recurrent ventricular tachyarrhythmias, and 20 patients continue to require drug therapy, it is possible that epicardial and endocardial mapping at operation may prove useful in better localizing and resecting the site of ventricular irritability, partially salvaging patients in this group.

Indications for epicardial mapping: Our results compare very favorably with those of other studies in which epicardial mapping was used[24,26,27] and raise the question of when the technique should be indicated. For example, 43 percent of our patients were asymptomatic and were receiving no antiarrhythmic medications at a mean follow-up time of 40.7 months. Of the 57 percent of patients receiving antiarrhythmic medications, only 4 (11 percent) had recurrent documented ventricular tachycardia. Of these, only two were symptomatic, whereas the other two had short bursts of ventricular tachycardia, lasting for seconds, and detected only by Holter monitoring. Whereas resection of ventricular aneurysms stopped the life-threatening ventricular tachycardia and fibrillation in our patients, ambulatory electrocardiographic monitoring[40] demonstrated that ventricular premature complexes still occurred. These results suggest that ventricular aneurysmectomy without the aid of epicardial mapping leads to satisfactory clinical results in the majority of patients.

Limitations of epicardial and endocardial mapping: Although epicardial and endocardial mapping techniques will play a role in the surgical management of patients in this category in the future, they are not without certain limitations, and their role is certainly the subject of controversy. First, mapping is a rather complex, rather time-consuming technique that will prolong the surgical procedure. However, with computer applications that will more rapidly display results of epicardial mapping, this disadvantage may be minimized. Second, the spontaneous occurrence of the arrhythmia or its induction with programmed stimulation is necessary during the operation for mapping to be accomplished. Third, there is recent evidence[27,39] suggesting that epicardial mapping may not be sufficient to identify or predict the endocardial origins of many ventricular tachyarrhythmias, but instead that endocardial or intramural mapping may be necessary preoperatively and intraoperatively to promote better definition of the reentry circuits. Although our study has identified a patient group that may potentially benefit from epicardial and endocardial mapping intraoperatively, the criteria for proper patient selection for this technique are unclear. Despite the potential benefits of both endocardial and epicardial mapping, the advantage of this technique over left ventricular aneurysmectomy without mapping remains unproved. For the present, we believe it is prudent to continue surgical resection guided by what is anatomically possible.

For the purpose of continued clinical study of patients who might benefit from surgery, we would propose the following evaluation protocol: (1) Patients should have documentation of the failure of medical therapy; (2) full hemodynamic and angiographic evaluation of ventricular function and coronary anatomy should be made; and (3) electrophysiologic studies with programmed arrhythmia induction and attempts to block the induction of arrhythmias with drugs should be made. When considerable experience has accumulated, the subgroups of patients needing mapping may be identified.

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Development of Pharmacodynamic Tolerance to Prazosin in Congestive Heart Failure

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In order to determine and compare the pharmacodynamic responses to single and multiple dose prazosin therapy in cardiac failure, 14 patients with severe low-output heart failure underwent central and regional hemodynamic measurements after random placement in one of two prazosin dosing schedules. A single 5 mg oral dose of prazosin (Group A, no. = 7) significantly increased the cardiac index and stroke volume index while significantly decreasing systemic, pulmonary and pulmonary capillary wedge pressures and vascular resistances. Hepatic plasma flow and limb blood flow increased after the single dose. Striking attenuation of these hemodynamic effects occurred when the same dose was administered after 24 hours of pretreatment with oral prazosin, 2 mg every 8 hours (Group B, no. = 7). The plasma prazosin levels of the two groups, drawn 2 hours after administration, were 24.5 and 30.5 ng/ml, respectively. Repeated administration of prazosin in patients with congestive heart failure results in rapid attenuation of its beneficial central and regional hemodynamic effects. The usefulness of this vasodilator as a preload- and afterload-reducing agent in the clinical setting of chronic congestive heart failure may be limited by the development of pharmacodynamic tolerance.

Reduction of preload and afterload in congestive heart failure after a single oral dose of prazosin has been demonstrated.[1,2] Attenuation of the beneficial central hemodynamic effects (for example, increased cardiac output, reduced left ventricular filling pressure) has been noted after several sequential doses of this vasodilator.[3–5] This study was designed to determine and compare the central and regional hemodynamic responses of prazosin after a single dose and after multiple sequential doses in the setting of congestive heart failure; plasma prazosin levels are provided.

Methods

Study patients: Fourteen adult patients with severe congestive heart failure were studied. The patients were randomly separated into two groups on the basis of the dosing schedule: Group A consisted of seven patients, four men and three women with a mean age of 56 years; four had ischemic congestive cardiomyopathy and three had idiopathic congestive cardiomyopathy. Group B consisted of seven men with a mean age of 60 years; five had ischemic congestive cardiomyopathy and two had idiopathic congestive cardiomyopathy. The diagnoses were confirmed with cardiac catheterization in all patients before the study. Use of diuretic agents and other vasodilators was discontinued a minimum of 48 hours before the study; all patients had received oral furosemide in doses of 40 to 200 mg daily and four patients in each group were taking oral isosorbide dinitrate, 80 mg daily. Administration of digitalis preparations and antiarrhythmic therapy were continued throughout the study period.

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Protocol: Written informed consent was obtained from each patient before the study. Patients in both Groups A and B underwent central hemodynamic studies every 6 hours during a 24 hour control period. Stability of the baseline hemodynamic measurements was ensured by not including patients whose cardiac index and pulmonary capillary wedge pressure demonstrated a coefficient of variation greater than 10 percent during the control period. The last set of measurements of the control period, which represented the immediate pre-prazosin determinations, were used as the control values. These values are provided in Table I for both groups. Patients in Group A then received 5 mg of prazosin orally and over the subsequent 8 hours underwent hourly hemodynamic measurements. After the control period, patients in Group B received 2 mg of prazosin orally every 8 hours for 24 hours followed by a 5 mg dose. Hemodynamic studies were performed hourly over 8 hours after administration of the latter dose. The last set of measurements of the control period served as the control values for Group B. (1) because these patients demonstrated little variation in their hemodynamic measurements over the 24 hour control period, and (2) because we wished to determine whether the pharmacodynamic responses elicited by prazosin are different for a single 5 mg dose than for the same dose after pretreatment with prazosin (three sequential doses of 2 mg every 8 hours).

Hemodynamic procedures and measurements: A triple lumen Swan-Ganz catheter was placed in the pulmonary artery of each patient before the control period. Measurements taken during the control period and after administration of prazosin included pulmonary arterial and pulmonary capillary wedge (pulmonary arterial occlusive) pressure obtained utilizing Electronics for Medicine M2101 pressure amplification units; cardiac output (in triplicate), obtained with the thermodilution technique using an Instrumentation Laboratory 601 computer and 602 recorder; and indirect systemic blood pressures, obtained with a calibrated sphygmomanometer. Mean systemic arterial pressure was derived using the formula: 1/3 of the pulse pressure plus diastolic pressure. Heart rate was determined from a monitor recording taken during the cardiac output measurements.

The following calculations were made: cardiac index (liters/min per m^2) = cardiac output/body surface area; stroke volume index (ml/beat per m^2) = cardiac index/heart rate; total systemic vascular resistance (dynes cm sec^{-5}) = mean systemic arterial pressure × 80/cardiac output (liters/min); and total pulmonary vascular resistance (dynes cm sec^{-5}) = mean pulmonary arterial pressure × 80/cardiac output (liters/min).

The regional hemodynamic measurements were made once for each patient during the control period and once 2 to 3 hours after the administration of prazosin. Hepatic plasma flow was determined from indocyanine green clearance data.[6,7] Para-aminohippurate clearance was used to determine renal plasma flow.[8] Limb blood flow (right upper limb) was measured in triplicate using venous occlusive plethysmography.

Plasma prazosin concentrations: Five mixed venous blood samples were drawn from each patient through the distal lumen of the pulmonary arterial catheter at 5 minute intervals precisely between 2 hours and 2 hours, 20 minutes after the administration of the 5 mg dose of prazosin; the plasma of the five samples for each patient was pooled for analysis. The concentration of prazosin in the plasma samples was determined with a modified form of a high pressure liquid chromatographic procedure using fluorescence detection.[9]

Analysis of variance and Student's *t* test for paired data were used in the statistical analysis.

TABLE I
Mean Control Values for the Central Hemodynamic and Regional Flow Measurements in the Two Groups (mean ± standard error of the mean)

	Normal Values*	Group A	Group B
Heart rate (beats/min)	—	86 ± 7	89 ± 3
Cardiac index (liters/min per m^2)	>2.75	2.00 ± 0.18	2.09 ± 0.10
Stroke volume index (ml/stroke per m^2)	—	25 ± 4	24 ± 2
Pulmonary capillary wedge pressure (mm Hg)	<15	26 ± 5	25 ± 2
Mean arterial pressure (mm Hg)	—	91 ± 5	88 ± 4
Mean pulmonary arterial pressure (mm Hg)	<25	34 ± 4	35 ± 3
Total systemic resistance (dynes $sec\ cm^{-5}$)	<1400	2113 ± 225	2011 ± 103
Total pulmonary resistance (dynes $sec\ cm^{-5}$)	<250	852 ± 123	748 ± 91
Hepatic plasma flow (ml/min)	>530	280 ± 84	321 ± 53
Renal plasma flow (ml/min)	>750	369 ± 51	390 ± 32
Limb blood flow (ml/100 ml tissue per min)	>6.0	3.81 ± 0.4	4.07 ± 0.6

* Derived from data obtained in our laboratory. Group A = seven patients who received a single 5 mg dose of prazosin. Group B = seven patients who received prazosin, 2 mg every 8 hours per 24 hours preceding the 5 mg dose. The control values for Group B were the last measurements before the pretreatment (2 mg every 8 hours) period.

Results

The control central and regional hemodynamic values for both groups are presented in Table I. There was no significant difference between any of the control study measurements of the two groups. The severity of heart failure in both groups was confirmed by the low mean cardiac and stroke volume indexes and the elevated values for mean pulmonary capillary wedge pressure and vascular resistance.

The central cardiovascular responses elicited by prazosin in the two groups are illustrated in Figures 1 and 2. A single 5 mg dose of prazosin (Group A) increased the mean cardiac and stroke volume indexes with a concomitant decrease of mean systemic and pulmonary arterial pressures, pulmonary capillary wedge pressures and total systemic and pulmonary vascular resistances. These changes were greatly attenuated in Group B. The hemodynamic responses of prazosin in Group B were actually less than the changes elicited by the first 2 mg dose of the pretreatment period (Fig. 1). *Oral administration of a single dose of 5 mg of prazosin (Group A) significantly increased hepatic plasma flow and limb blood flow (Fig. 3).* Multiple dosing (Group B) resulted in attenuation of these regional hemodynamic effects. Renal plasma flow was not significantly altered in either group.

The plasma prazosin levels of Groups A and B were not significantly different (Fig. 4).

Discussion

Mechanism of tolerance development: Single dose oral prazosin therapy improved the central hemody-

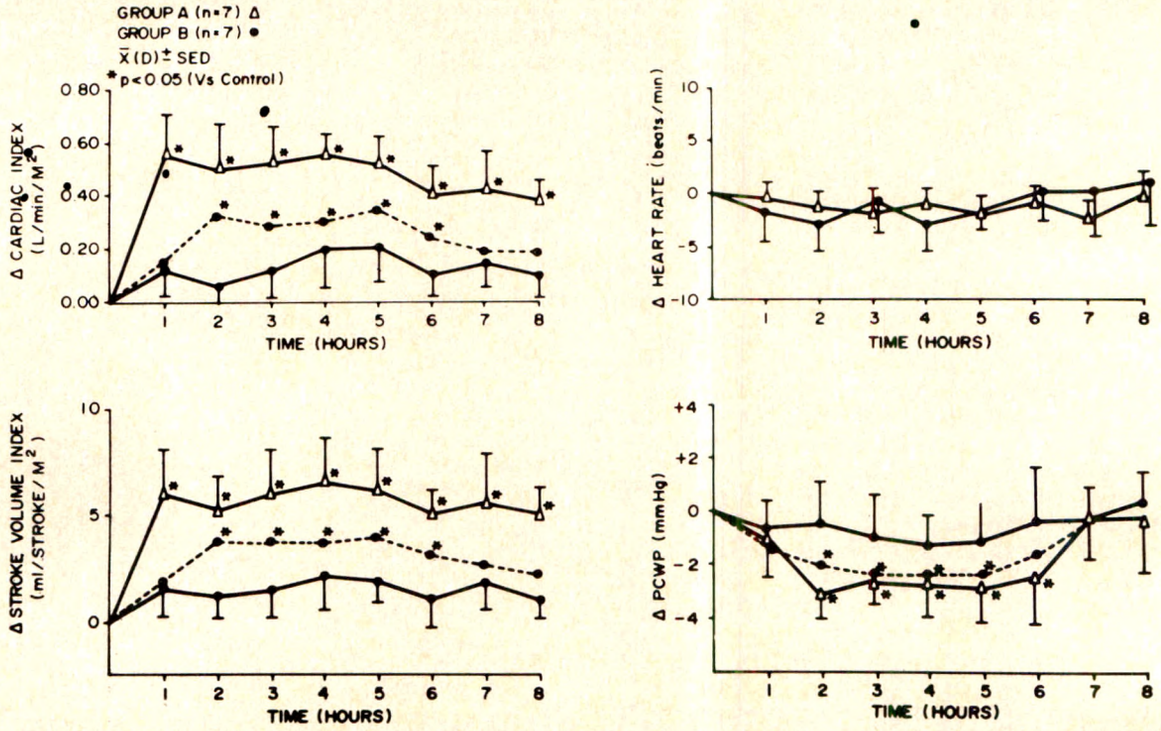

FIGURE 1. Graphs illustrating the changes in cardiac index, stroke volume index, heart rate and pulmonary capillary wedge pressure (PCWP), after oral prazosin administration in the two groups. A single 5 mg dose of prazosin (Group A) significantly increased the cardiac index and stroke volume index and decreased the pulmonary capillary wedge pressure. Five mg of prazosin administered after a 24 hour period of pretreatment with prazosin (Group B) did not significantly change these variables from the baseline values. Heart rate was not significantly altered in either group. The changes in cardiac index, stroke volume index and pulmonary capillary wedge pressure with the first 2 mg dose in Group B are presented as **dashed lines.** (Control values for the 2 mg response of Group B are presented in Table I, Group B) L = liters; M = meters; p = probability; $\bar{x}(D) \pm SED$ = mean difference ± standard error of the difference.

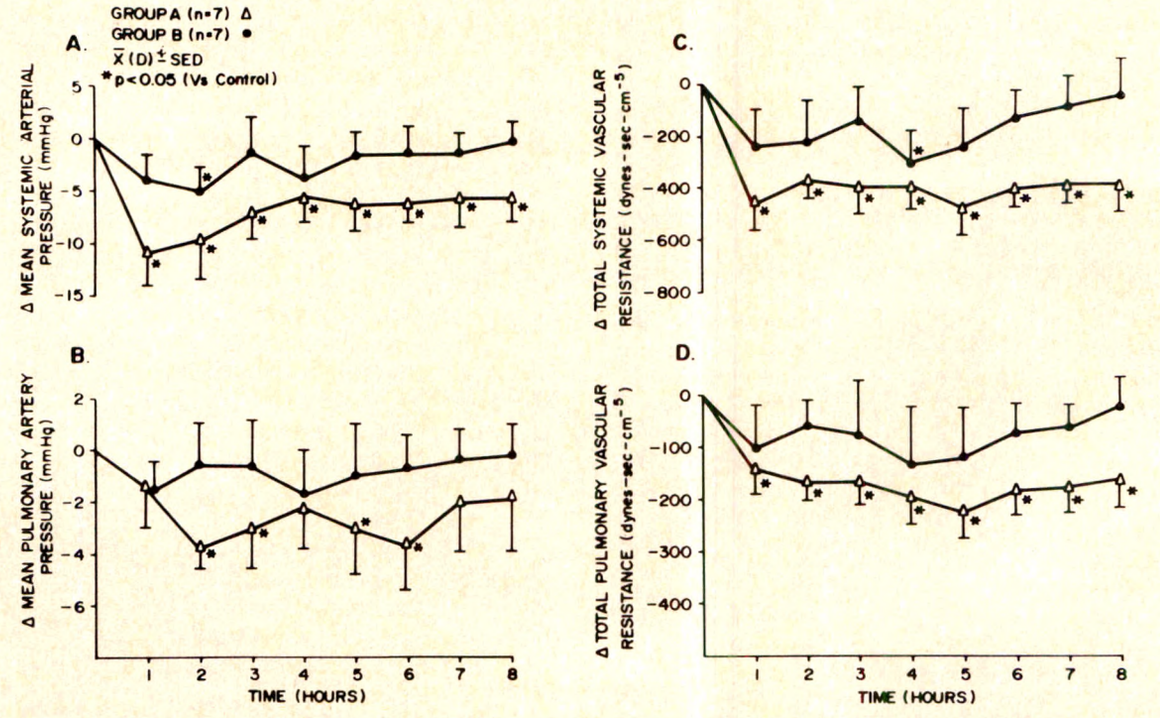

FIGURE 2. Mean systemic arterial pressure (**A**), pulmonary arterial pressure (**B**), and total systemic (**C**) and pulmonary (**D**) vascular resistances decreased significantly after single dose prazosin therapy in Group A. These effects were attenuated in Group B (multiple-sequential dosing). Δ = change; other abbreviations as in Figure 1.

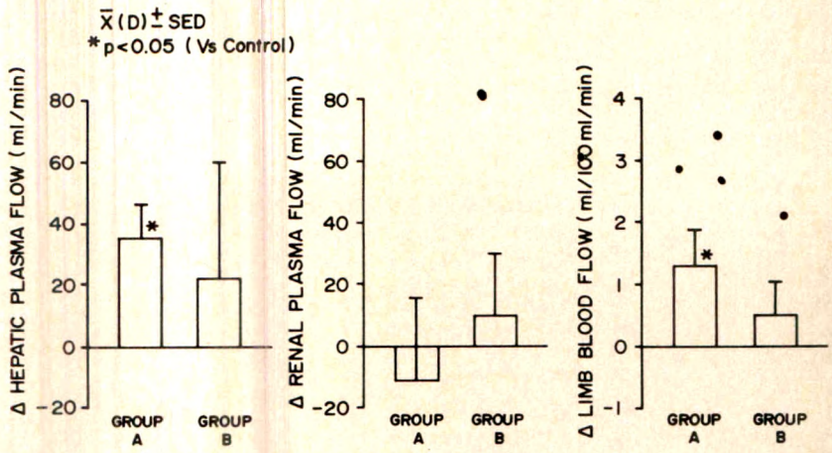

FIGURE 3. A single 5 mg dose of prazosin (Group A) significantly increased mean hepatic plasma flow and limb blood flow. The changes returned toward baseline after repeated administration (Group B). Renal plasma flow was not significantly altered in either group. Abbreviations as in Figures 1 and 2.

namics in these patients with severe cardiac failure. An increase in hepatic plasma flow and limb blood flow was also demonstrated with the single 5 mg dose of this drug. With multiple-sequential administration, the central hemodynamic measurements did not change from the baseline values. The hepatic plasma flow and limb blood flow responses seen with single dose prazosin also diminished with repeated administration; this was probably secondary to the attenuation of certain central hemodynamic variables, specifically the cardiac index and vascular resistance changes. The central and regional hemodynamic attenuation demonstrated in Group B (multiple-sequential administration) occurred with a mean plasma prazosin concentration similar to that of Group A (single dose administration); this finding implicates the development of true drug tolerance. Although the mechanism for the development of this pharmacodynamic tolerance is not known at present, the plasma prazosin concentration data refute the concept of an accelerated disposition process such as that which occurs with hepatic enzyme induction. It is noteworthy that in Group B the central hemodynamic effects of the 2 mg dose of prazosin were greater than those of the 5 mg dose, given subsequently; this indicates that simply increasing the dose of prazosin will not necessarily overcome the attenuation.

Therapeutic implications: Recent reports of improved exercise tolerance[2,10,11] and exercise hemodynamics[11] with prazosin in congestive heart failure suggest that this drug may retain a role in the treatment of heart failure despite the development of attenuation of resting hemodynamics with repeated doses. However,

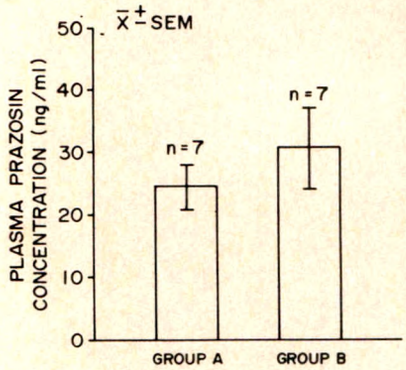

FIGURE 4. The plasma prazosin levels of the two groups were not significantly different. n = number of patients; other abbreviations as in Figure 1.

the attenuation of the resting (nonexercise) hemodynamic effects with the long-term administration of prazosin may preclude its application in patients with symptoms of congestion and low cardiac output at rest. In patients with symptoms of heart failure at rest, an agent that elicits a persistent improvement of resting hemodynamics (as well as tolerance for activity) during long-term administration would be preferable.

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Influence of Short-Term Oral Hydralazine Therapy on Exercise Hemodynamics in Patients with Severe Chronic Heart Failure

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Changes in left ventricular performance were evaluated in 14 patients with functional New York Heart Association class III or IV chronic heart failure before and after the addition of oral hydralazine to conventional therapy. With conventional therapy, cardiac output increased from 3.4 ± 0.8 (mean ± 1 standard deviation) at rest to 4.7 ± 1.4 liters/min during exercise. This increase in cardiac output on exercise during conventional therapy was mainly due to an increase in heart rate. After the addition of hydralazine, cardiac output at rest increased to 5.0 ± 1.4 liters/min. The increase in cardiac output was essentially due to an increase in stroke volume. This enhanced stroke volume after hydralazine therapy was maintained during exercise. Hydralazine therapy did not change either the left ventricular filling pressure at rest or the magnitude of increase in left ventricular filling pressure during exercise. Nevertheless, increased cardiac output and stroke volume with similar changes in left ventricular filling pressure during exercise indicated improved left ventricular performance after hydralazine therapy. After short-term hydralazine therapy, symptom-limited peak exercise work load, duration of exercise and maximal oxygen consumption during exercise did not increase. Clinical follow-up at 2 months after long-term therapy revealed subjective improvement in exercise tolerance in 13 of the 14 patients.

That the use of vasodilator agents is a rational approach for the management of heart failure seems to be established.[1–3] Beneficial hemodynamic and clinical responses to various intravenous vasodilator agents in patients with acute heart failure have been documented.[4–16] For long-term treatment of patients with chronic congestive heart failure, the hemodynamic effects of many nonparenteral vasodilator agents have also been evaluated.[11–18] Recent studies[19–22] have demonstrated that with the use of oral hydralazine, significant improvement occurs in the hemodynamics at rest of patients with chronic heart failure.

However, patients with chronic heart failure may remain relatively asymptomatic at rest, and symptoms related to low cardiac output or increased pulmonary venous pressure, or both, may be manifested only during exercise. Furthermore, cardiac performance at rest may not be severely depressed in many of these patients; marked deterioration of cardiac function may occur in the same patients in response to exercise-induced stress.[23] It is apparent, therefore, that to evaluate the efficacy of any therapeutic agent for the management of chronic heart failure, it is desirable to assess not only the changes in resting hemodynamics but also the changes in exercise hemodynamics. Although oral hydralazine therapy produces beneficial changes in hemodynamics at

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rest, information regarding the changes in exercise hemodynamics are scanty. The purpose of this study was to evaluate the effects of short-term oral hydralazine therapy on cardiac performance during exercise.

Methods

Patients: Fourteen patients with chronic left heart failure, who were symptomatic at rest or with minimal activity (New York Heart Association functional class III or IV)[24] despite optimal conventional therapy were selected from an outpatient group. These patients had a history of stable symptoms of severe heart failure for at least 2 months (taking the same doses of digitalis and diuretics) before entry into this study. Also, they had symptoms of heart failure for a median duration of 4 years (range 6 months to 10 years) before entry into this study. Significant mitral regurgitation was not clinically apparent in any of these patients. No patient was receiving any antihypertensive medication at the time of the study. Patients were hospitalized in the coronary care unit for the duration of the study, maintained on stable dosages of digitalis and diuretic drugs and restricted in dietary sodium intake. On admission for this study, the median serum digoxin level was 1.5 ng/ml (range 1.2 to 2.2) and the median furosemide dosage was 160 mg/day (range 80 to 320). The causes of heart failure were coronary heart disease in nine patients and cardiomyopathy of unknown origin in five patients.

Hemodynamic measurements: Right atrial, pulmonary arterial and pulmonary capillary wedge pressures were measured from an indwelling Swan-Ganz catheter inserted percutaneously from the internal jugular or subclavian vein. Cardiac output in triplicate (standard deviation ± 5 percent) was determined with use of the thermodilution technique using the same catheter. Left ventricular filling pressure was estimated from the mean pulmonary wedge or pulmonary arterial diastolic pressure, the method remaining constant in each patient. Blood pressure was measured from an indwelling radial arterial catheter. Heart rate was determined from the electrocardiogram simultaneously with cardiac output. Total systemic vascular resistance (TSVR) in dynes sec cm^{-5} was calculated as $TSVR = (\overline{AP} - \overline{RA}/CO) \times 80$, where $\overline{AP}$ = mean arterial pressure, $\overline{RA}$ = mean right atrial pressure, and CO = cardiac output.

Oxygen saturations were determined from oximetry (American Optical, Buffalo, New York), and the very low

TABLE I

Hemodynamic Measurements

Case no.	Age (yr)	Therapy*	CO (liters/min)	a-v O_2 (ml/100 ml)	SV (ml)	HR (min^{-})	LVFP (mm Hg)	$\dot{V}O_2$ (ml/min)	$\overline{AP}$ (mm Hg)	TSVR (dynes sec cm^{-5})	$\overline{PA}$ (mm Hg)	$\overline{RA}$ (mm Hg)	W (kp-m)	H (mg)
1	46	CR	2.1	8.8	31	67	28	184.8	75	2476	40	10	—	—
		CE	3.4	10.6	45	75	28	360.4	75	1388	45	16	150	—
		HR	5.0	3.2	71	70	30	160.0	80	1088	43	12	—	75
		HE	5.1	7.6	68	75	30	387.6	80	988	48	17	150	75
2	65	CR	2.8	6.5	37	76	20	182.0	110	2971	26	6	—	—
		CE	4.5	9.2	50	90	25	414.0	100	1653	35	7	150	—
		HR	6.2	4.1	75	83	12	254.2	75	916	21	4	—	50
		HE	6.9	7.0	72	96	24	483.0	80	870	35	5	150	50
3	52	CR	3.2	6.1	38	84	40	195.2	91	2025	50	10	—	—
		CE	4.4	10.3	35	125	48	453.2	105	1691	67	12	200	—
		HR	3.4	5.4	45	76	32	183.6	80	1694	43	8	—	75
		HE	5.0	8.8	36	138	40	440.0	105	1344	65	21	200	75
4	52	CR	3.2	6.8	34	93	24	217.6	78	1475	38	19	—	—
		CE	3.3	10.3	31	108	33	339.9	90	1382	45	33	100	—
		HR	5.0	4.1	52	96	22	205.0	70	789	35	21	—	50
		HE	5.2	8.1	47	110	30	421.2	83	846	45	28	100	50
5	77	CR	3.1	6.7	32	97	12	207.7	90	2245	25	3	—	—
		CE	4.5	9.9	39	116	27	445.5	105	1600	47	15	100	—
		HR	3.8	4.9	38	99	13	186.2	95	1958	33	2	—	75
		HE	4.7	10.8	39	120	29	507.6	110	1753	55	7	100	75
6	70	CR	3.0	7.6	29	104	35	228.0	83	1413	45	30	—	—
		CE	3.3	10.6	22	148	40	349.8	100	1478	55	39	50	—
		HR	3.4	6.8	25	135	42	231.2	80	1012	52	37	—	75
		HE	3.9	8.6	27	143	43	335.4	85	821	58	45	50	75
7	71	CR	3.0	—	53	57	12	—	93	2400	20	3	—	—
		CE	3.4	—	35	96	28	—	107	2353	40	7	100	—
		HR	3.6	—	51	70	17	—	87	1756	25	8	—	75
		HE	4.4	—	42	104	30	—	101	1600	50	13	100	75
8	46	CR	3.9	5.0	46	84	15	195.0	90	1744	27	5	—	—
		CE	7.6	9.0	58	132	30	684.0	115	1116	55	9	400	—
		HR	5.6	4.3	58	96	22	240.8	85	1143	22	5	—	100
		HE	8.9	6.5	65	138	32	578.5	100	818	52	9	400	100
9	59	CR	5.2	6.5	37	140	16	338.0	75	1138	33	9	—	—
		CE	6.5	13.1	40	164	35	851.5	100	960	49	22	300	—
		HR	6.4	5.2	53	120	18	332.8	75	788	30	10	—	75
		HE	8.9	9.5	51	175	28	845.5	85	629	41	15	350	75

continued

TABLE I (Continued)

Case no.	Age (yr)	Therapy*	CO (liters/min)	a-v O_2 (ml/100 ml)	SV (ml)	HR (min^{-})	LVFP (mm Hg)	VO_2 (ml/min)	$\overline{AP}$ (mm Hg)	TSVR (dynes sec cm^{-5})	$\overline{PA}$ (mm Hg)	$\overline{RA}$ (mm Hg)	W (kp-m)	H (mg)
10	82	CR	3.4	4.3	49	70	23	146.2	95	2071	35	17	—	—
		CE	3.7	9.5	51	72	30	351.2	110	1839	40	25	150	—
		HR	3.2	3.6	44	71	23	115.2	100	2200	33	12	—	75
		HE	4.2	8.5	57	74	28	357.0	117	1714	42	27	150	75
11	46	CR	2.8	5.4	27	103	22	151.2	77	2029	33	6	—	—
		CE	4.8	12.4	36	132	35	595.2	105	1500	50	15	300	—
		HR	5.6	3.4	51	109	20	190.4	75	1014	27	4	—	75
		HE	6.2	11.3	45	138	40	700.6	100	1096	55	15	300	75
12	65	CR	4.3	6.3	49	87	25	270.9	100	1730	38	7	—	—
		CE	6.4	12.8	52	123	38	819.2	115	1300	60	11	300	—
		HR	7.4	4.1	80	93	15	303.4	80	811	24	5	—	75
		HE	8.1	10.6	61	132	40	858.6	115	1067	65	7	300	75
13	70	CR	3.6	4.5	47	76	9	162.0	83	1778	15	3	—	—
		CE	3.7	8.8	37	99	35	325.6	92	1859	40	8	100	—
		HR	4.7	2.9	52	90	7	136.3	83	1294	14	7	—	75
		HE	4.9	7.9	41	120	33	387.1	97	1420	37	10	100	75
14	46	CR	4.2	7.2	41	102	28	302.4	75	1238	36	10	—	—
		CE	6.2	11.7	47	132	38	725.4	85	903	45	15	250	—
		HR	7.0	5.0	70	100	25	350.0	80	834	33	7	—	75
		HE	7.6	10.8	59	128	35	820.8	105	895	47	20	250	75
Averages (mean ± SD)														
		CR	3.4 ±0.8	6.3 ±1.3	39 ±8	89 ±21	22 ±9	213 ±58	87 ±11	1910 ±512	33 ±10	10 ±8	—	
		CE	4.7 ±1.4	10.6 ±1.4	41 ±10	115 ±27	34 ±6	517 ±193	100 ±11	1502 ±383	48 ±9	17 ±10	189 ±104	
		HR	5.0 ±1.4	4.4 ±1.1	55 ±15	93 ±19	21 ±9	222 ±73	82 ±8	1235 ±473	31 ±10	10 ±9	—	
		HE	6.0 ±1.8	8.9 ±1.6	51 ±13	121 ±27	33 ±6	548 ±194	97 ±13	1133 ±367	50 ±9	17 ±11	193 ±109	
Significance Level of Statistical Comparisons†														
		CR-HR	< 0.01	< 0.01	< 0.01	NS	NS	NS	< 0.05	< 0.01	NS	NS	—	
		CE-HE	< 0.01	< 0.01	NS	—	NS	NS	NS	< 0.01	—	NS	NS	

*Conventional therapy (C) compared with hydralazine (H) at rest (R) and during exercise (E).
$\overline{AP}$ = mean arterial pressure; a-v O_2 = arteriovenous oxygen differences; CO = cardiac output; H = peak hydralazine dose at which variables were measured. HR = heart rate; LVFP = left ventricular filling pressure; NS = not significant; $\overline{PA}$ = mean pulmonary artery pressure; $\overline{RA}$ = mean right arterial pressure; SD = standard deviation; SV = stroke volume; TSVR = total systemic vascular resistance; VO_2 = oxygen consumption; W = peak exercise work load.
† The significance level (p) compares the two therapies at rest and at exercise.

mixed venous saturations frequently obtained during exercise were verified by blood gas analysis (Corning, Medfield, Massachusetts),[25] or oxygen content determinations,[26] and were in agreement within ±5 percent. Arteriovenous oxygen difference (a-v O_2) in ml/100 ml was calculated as: a-v O_2 = $(a_{sat} - Pa_{sat}) \times 1.34 \times Hgb$, where a_{sat} and Pa_{sat} = arterial and mixed venous (pulmonary arterial) saturations, respectively, and Hgb = hemoglobin concentration.

Arterial or mixed venous lactate determinations[27] were made at rest and during exercise in seven patients, after we reconfirmed that no lactate extraction occured across the pulmonary circulation.[28]

Exercise protocol: Sequential measurements at rest and during exercise were performed at the same time of day in the exercise laboratory with the patient in the postabsorptive state. After at least 15 minutes of acclimation, measurements were performed with the patient supine during conventional therapy. The patient's feet were then secured to the pedals of a bicycle ergometer with the center of the crank 12 cm above the table level. Progressive bicycle exercise was performed to a symptom-limited maximum. The initial work load was 50 kilopond meters (kpm) in seven patients who had class IV heart failure and 100 kpm in seven patients who had class III heart failure. All patients exercised 3 minutes at their initial work load level and then at work loads that were successively increased by 50 kpm increments every 3 minutes. All patients pedaled at 40 revolutions/min to ensure a constant work load. Hemodynamic variables were measured at peak exercise effort. All patients reported symptoms at peak exercise of severe general body fatigue, severe leg discomfort and moderate to severe dyspnea; one patient also reported angina. No patient was able to identify any of these symptoms as the reason for stopping exercise. Lactate measurements in seven of these patients revealed a substantial elevation at peak exercise. We believed therefore that this represented good exercise effort, even without measurements of maximal oxygen uptake.

Hydralazine protocol: Patients were then returned to the coronary care unit for continuous hemodynamic monitoring at rest and for initiation of hydralazine therapy. Other drug therapy, including administration of digoxin and furosemide, was kept constant during the addition of hydralazine therapy. The initial dose of hydralazine was 25 mg. Subsequent doses were administered every 6 hours, and increments of 25 mg were added. We[19] have previously reported that there is no

first dose effect of oral hydralazine on cardiac output and that careful repeated hemodynamic measurements during repeated doses must be made before a sustained effect is observed. We have also observed, but not reported, that resting hemodynamics of patients with chronic severe heart failure on conventional drug therapy are stable over a 1 to 3 day period. We therefore used a physiologic end point to hydralazine therapy before the patient exercised. This end point required a sustained increase in cardiac output of at least 10 percent greater than baseline measurements over a 12 hour period. In our patients, this physiologic end point required a median time of 36 hours of hydralazine therapy (range 24 to 48 hours), a median dose of 75 mg of hydralazine administered every 6 hours (range 50 to 100 mg every 6 hours) and a median total dose of 400 mg of hydralazine (range 275 to 775 mg). Patients then duplicated the exercise protocol used before taking hydralazine 2 hours after the last dose of hydralazine. Measurements were made at peak work load.

Statistics: Comparisons between conventional therapy and hydralazine both at rest and during exercise were made using the paired *t* statistic.

Results

Cardiac output: Individual patient data are summarized in Table I. During conventional therapy, cardiac output increased from 3.4 ± 0.8 at rest to 4.7 ± 1.4 liter/min at peak exercise. When hydralazine was added, cardiac output increased from 5.0 ± 1.4 at rest to 6.0 ± 1.8 liter/min at peak exercise. Hydralazine therapy caused statistically significant increases in cardiac output (Fig. 1) both at rest and during exercise ($P < 0.01$). For most patients, the increases in cardiac output during hydralazine therapy at rest were also sustained during exercise.

Contributions to cardiac output were assessed from heart rate and stroke volume (Fig. 2). Hydralazine increased heart rate 4 percent at rest and 5 percent at peak exercise. However, this increase was not statistically significant. Stroke volume was 39 ± 8 ml at rest and remained unchanged (41 ± 10 ml) during exercise on conventional therapy. After the addition of hydralazine, stroke volume at rest increased to 55 ± 15 ml and remained elevated (51 ± 13 ml) during exercise.

Mixed venous oxygen saturation and oxygen consumption: During conventional therapy, mixed venous oxygen saturation decreased from 58.2 ± 7.6 at rest to 35.3 ± 7.0 percent at peak exercise. When hydralazine was added, mixed venous oxygen saturation at rest increased (69.5 ± 6.9 percent) concurrent with an increase in cardiac output. During peak exercise, the decrease in mixed venous oxygen saturation (46.7 ± 7.5 percent) was also less than that during conventional therapy alone. Thus, hydralazine caused statistically significant increases in mixed venous oxygen saturation both at rest and during exercise ($P < 0.01$). We found that arterial blood remained fully saturated both at rest and during exercise.

During conventional therapy, oxygen consumption (a product of cardiac output and arteriovenous oxygen difference) increased from 214 ± 58 at rest to 517 ± 193 ml/min at peak exercise. With the addition of hydralazine, oxygen consumption increased from 222 ± 73 at rest to 548 ± 194 ml/min at peak exercise. Hydralazine therapy did not cause statistically significant changes in oxygen consumption either at rest or during exercise

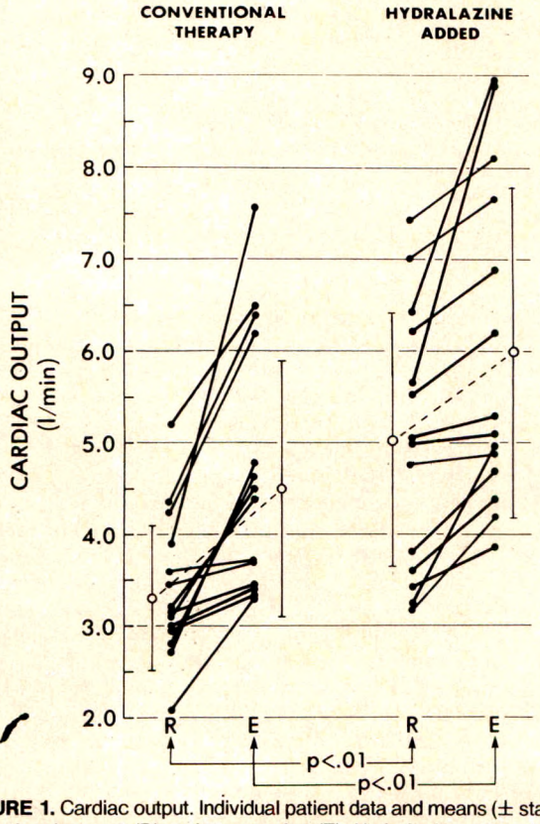

FIGURE 1. Cardiac output. Individual patient data and means (± standard deviations) at rest (R) and at exercise (E). Hydralazine caused an increase in cardiac output at rest as well as during exercise. l = liter; p = probability.

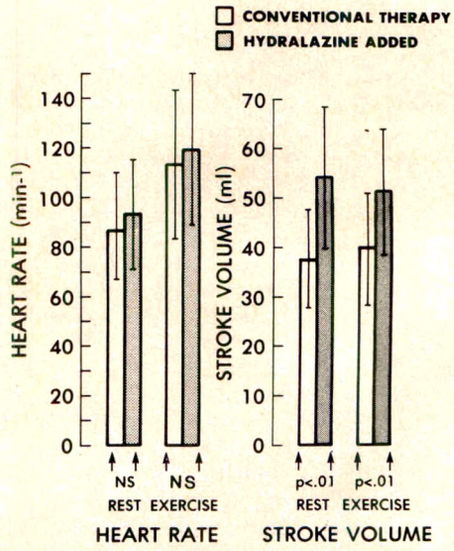

FIGURE 2. Contributions to cardiac output. Means (± standard deviations) of heart rate and stroke volume. Hydralazine caused small increases in stroke volume. NS = not significant; p = probability.

($P < 0.2$) (Fig. 3). Therefore, although hydralazine increased cardiac output, oxygen consumption remained unchanged because arteriovenous oxygen difference decreased (Table I).

Systemic and cardiac pressures: During conventional therapy, mean arterial pressure increased from 87 ± 11 at rest to 100 ± 11 mm Hg at peak exercise. During hydralazine therapy, mean arterial pressure increased from 82 ± 8 at rest to 97 ± 13 mm Hg at peak exercise. There was a small but statistically significant decrease in resting blood pressure when hydralazine was added ($P < 0.05$). There was no statistically significant decrease in mean arterial pressure at peak exercise when hydralazine was added ($P > 0.10$). During conventional therapy, total systemic vascular resistance decreased from 1,910 ± 512 at rest to 1,502 ± 383 dynes sec cm^{-5} at peak exercise. During therapy with hydralazine, the total systemic vascular resistance decreased from 1,235 ± 475 at rest to 1,133 ± 367 dynes sec cm^{-5} at peak exercise. There was a statistically significant decrease in total systemic vascular resistance during hydralazine therapy both at rest and during exercise ($P < 0.01$). Changes in stroke volume during exercise were significantly correlated with changes in systemic vascular resistance, both on conventional therapy ($r = -0.82$) and on hydralazine ($r = -0.78$).

We found that right atrial, mean pulmonary arterial and mean pulmonary wedge pressures at rest were elevated in these patients with heart failure during conventional therapy. Hydralazine did not affect any of these intracardiac pressures (Table I) either at rest or at peak exercise.

Exercise work load and metabolism: During conventional therapy, the average peak exercise work load was 189 ± 104 kpm, and total pedaling time was 11.3 ± 4.4 minutes. After addition of hydralazine, the work load was 193 ± 109 kpm and the total pedaling time was 11.3 ± 4.5 minutes. There was no statistically significant difference between the work loads or the total pedaling times ($P > 0.2$).

Serum lactate was used as a marker of effort during exercise. During conventional therapy, serum lactate increased an average of 31.1 ± 17.5 mg/100 ml during exercise. The increase in serum lactate averaged 26.4 ± 17.2 mg/100 ml during exercise after the addition of hydralazine. There was no statistically significant difference between the lactate levels at rest or during exercise ($P > 0.1$).

Clinical follow-up during long-term hydralazine therapy: Clinical reassessment was made at an initial 2 month follow-up. Thirteen of the 14 patients showed improvement. All seven patients who initially had class IV heart failure showed improvement to class III. One of these patients was then considered stable enough to undergo left ventricular aneurysmectomy and coronary arterial bypass surgery. Six of the seven patients who initially had class III heart failure showed improvement—four patients to class II and two patients to class I. One of these seven patients discontinued hydralazine therapy shortly after hospital discharge because of intractable headaches.

Discussion

This study confirms previous reports that oral hydralazine produces beneficial changes in hemodynamics at rest in patients with chronic congestive heart failure. Thus, as previously reported,[19,20] after hydralazine therapy there was an increase (47 percent) in cardiac output and a decrease (−35 percent) in systemic vascular resistance. The increase in resting cardiac output was primarily due to an increase in stroke volume (41 percent). Left ventricular filling pressure did not decrease, presumably because hydralazine is a predominantly arteriolar dilator and does not cause significant peripheral venodilatation. However, an increase in cardiac output and stroke volume without any significant change in left ventricular filling pressure indicates improved left ventricular performance at rest.

Cardiac performance during exercise after hydralazine: The principal purpose of this study was to evaluate the influence of short-term oral hydralazine therapy on cardiac performance during exercise in patients with chronic heart failure. After the addition of hydralazine, cardiac output at peak exercise was greater in almost all patients than during conventional therapy. There was a significant increase in stroke volume in all patients, and this increase was maintained during exercise. Left ventricular stroke work index at rest and during exercise was also greater after the addition of hydralazine than during conventional therapy.

There was no significant change in resting left ventricular filling pressure after hydralazine therapy, and the magnitude of increase in left ventricular filling pressure from rest to exercise, both before and after the addition of hydralazine, was also similar. This finding is not unexpected because hydralazine is predominantly an arteriolar dilator. Although there was no change in

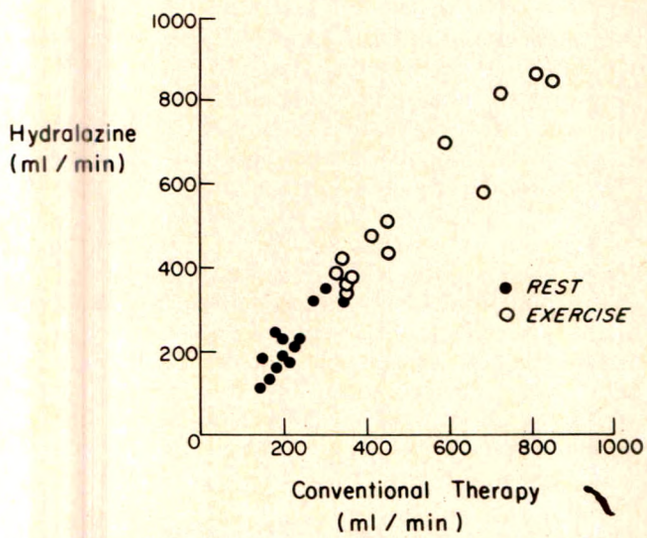

FIGURE 3. Oxygen consumption (ml/min) at rest (**closed circles**) and at peak exercise (**open circles**) in 13 of the 14 patients during conventional therapy and after the addition of oral hydralazine. Oxygen consumption did not change during short-term therapy with hydralazine in these patients.

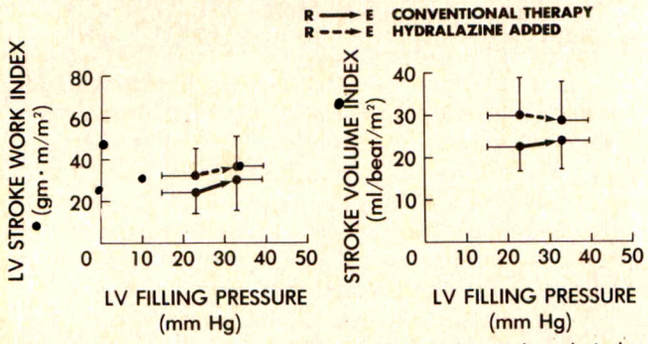

FIGURE 4. Changes in left ventricular (LV) stroke work and stroke volume indexes as well as changes in left ventricular filling pressure during exercise (E) with conventional therapy and after the addition of oral hydralazine. Increased stroke volume and stroke work indexes without any significant change in left ventricular filling pressure indicated improved left ventricular function with hydralazine therapy. R = rest; gm·m = gram-meter.

left ventricular filling pressure, stroke volume and stroke work index remained elevated during exercise, indicating a parallel and upward shift of left ventricular function curve (Fig. 4). Such a shift in left ventricular function curve suggests improved cardiac performance during hydralazine therapy not only at rest but also during exercise.

Oxygen consumption and aerobic exercise limits: Although exercise hemodynamics were better, maximal exercise was not altered by short-term hydralazine therapy in the patients studied. Exercise duration and peak symptom-limited exercise work loads in individual patients did not change. Oxygen consumption during exercise also remained unchanged after the addition of hydralazine to conventional therapy. Lower cardiac output during conventional therapy was associated with a higher oxygen extraction (widened arteriovenous oxygen difference and lower mixed venous oxygen saturation). After acute administration of hydralazine, with an increase in cardiac output, there was a concomitant decrease in arteriovenous oxygen difference; thus, oxygen consumption remained unchanged. It is probable that these patients achieved aerobic exercise limits. Mixed venous lactate concentrations during exercise were quite increased and similar both before and after the addition of hydralazine to conventional therapy, suggesting that aerobic limits were achieved during exercise after acute hydralazine therapy.

Maximal exercise capacity after hydralazine: Little or no increase in oxygen consumption or in the maximal exercise capacity of patients with chronic heart failure, despite improved cardiac performance, does not appear to be unique to acute hydralazine therapy. Similar results have been reported after short-term therapy with other pharmacologic agents such as nitrates and nitroglycerin,[29,31] prazosin[32] and salbutamol.[33] Lack of increase in maximal exercise capacity after acute hydralazine therapy may partly be explained by the increase in pulmonary venous pressure to an almost identical level with or without hydralazine; this pressure is an important determinant of dyspnea, which limited this exercise in many patients. However, nitrates, which are expected to decrease pulmonary venous pressure when added to hydralazine, do not apparently increase oxygen consumption or maximal exercise tolerance after short-term therapy in patients with chronic heart failure.[34] Left ventricular outflow resistance decreases during dynamic exercise as a result of arteriolar dilatation in exercising muscles.[35] Vasodilator therapy may not augment this exercise-induced vasodilatation.[29] However, in this study systemic vascular resistance at peak exercise after acute hydralazine therapy was significantly lower than that during conventional therapy, although the peak work load was almost identical.

It therefore remains unclear, why, despite an increase in cardiac output, oxygen consumption during exercise did not increase in our patients after short-term therapy with hydralazine. Changes in exercise hemodynamics, oxygen consumption and exercise tolerance during short-term therapy with any pharmacologic agent in patients with chronic heart failure may not be similar to those changes that might occur after long-term therapy with the same agent. Initial clinical evaluation indicated that 12 patients had subjective improvement in exercise tolerance. It is thus possible that changes in exercise capacity after long-term therapy with hydralazine may be different from changes that occur during acute intervention. However, further investigation will be needed to delineate more precisely the differences in exercise hemodynamics during short-term and long-term therapy with hydralazine in patients with chronic congestive heart failure.

Implications: Our study has demonstrated that acute oral therapy with hydralazine in patients with chronic congestive heart failure improves cardiac performance not only at rest but also during exercise. However, after short-term therapy, exercise capacity and oxygen consumption do not increase despite improved cardiac function. After long-term therapy, exercise tolerance may improve subjectively, at least in some patients. Further studies will be needed to evaluate the influence of such therapy on exercise hemodynamics in patients with chronic congestive heart failure.

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Pharmacokinetics of Digoxin in Patients With Acute Myocardial Infarction

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The effects of acute myocardial infarction on the pharmacokinetics of digoxin were studied. Digoxin, 0.75 mg, was given orally to 12 patients with left-sided cardiac failure due to acute myocardial infarction and to 9 healthy control subjects. Serum concentration of digoxin in the first 4 hours and the area under the serum concentration-time curve in the first 12 hours after administration of the drug were lower in patients with infarction than in control subjects ($P < 0.01$). The 24 hour area under the concentration curve, the amount excreted in urine and the renal clearance did not differ between the groups. The 24 hour area under the concentration curve correlated with the predigoxin pulmonary capillary wedge pressure and with heart rate ($P < 0.01$). The decrease of renal clearance of digoxin was related to the serum activity of MB isoenzyme of creatine kinase ($P < 0.001$). Morphine reduced and delayed the peak serum concentrations of digoxin ($P < 0.001$). Thus, the absorption of oral digoxin was slower and the peak concentrations remained lower in patients with acute myocardial infarction than in healthy control subjects. However, the total amount of digoxin absorbed was unchanged.

Knowledge about the influence of heart failure on the pharmacokinetics of drugs is surprisingly scant compared with information on the effect of hepatic or renal diseases.[1] Most studies on heart failure have concentrated on lidocaine, demonstrating changes in the apparent volume of distribution and clearance of the drug.[2] The few studies performed with digoxin had contradictory results. Heart failure was thought to cause delayed drug absorption[3] or to have no effect[4] on the pharmacokinetics of digoxin.

Because the knowledge of digoxin absorption and elimination in patients with acute myocardial infarction with left ventricular failure is of obvious importance in planning a rational dosage regimen we have performed a pharmacokinetic study of digoxin in a group of such patients.

Methods

Subjects: The study group consisted of 12 patients with acute myocardial infarction. All patients had normal renal function on the basis of normal creatinine clearance values. Relevant clinical characteristics are given in Table I. The diagnosis of acute myocardial infarction was based on history, electrocardiograms and serum enzyme activity levels. The patients were monitored in a coronary care unit and digoxin was given as part of routine medical care for left ventricular failure. All patients had clinical and radiologic signs of left-sided heart failure. Pulmonary capillary wedge pressures (obtained with Swan-Ganz catheterization) were elevated, but the values for cardiac output (by thermodilution technique) were within normal limits (Table II). No cardiogenic shock occurred. Only one patient (Case 11) had had a previous infarction.

The control group consisted of nine volunteers who had no evidence of cardiac, hepatic or renal diseases (Table I). Informed written consent was obtained from patients and volunteers before the study. No complications occurred during the study and there was no mortality during the hospital stay.

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TABLE I

Clinical Data in 12 Patients With Acute Myocardial Infarction and 9 Healthy Control Subjects

Case no.	Age (yr) & Sex	Weight (kg)	Infarct Site	Serum Enzyme Activity (units/liter) CK	MB	HBD	Serum Creatinine (mg/100 ml)	Creatinine Clearance (ml/min)	Drug Treatment During the Study
1	56F	77	Ant	511	14	487	0.80	126	Morphine 4 mg, 4 hr before digoxin
2	55M	58	Ant	207	17	364	0.95	96	Morphine 4 mg, 6 hr before digoxin
3	33M	68	Inf	2654	276	751	0.93	126	Diazepam 10 mg, 3 hr before digoxin
4	66M	80	Inf	64	*	376	1.05	102	. . .
5	65F	70	Ant	447	66	394	0.86	90	Morphine 4 mg, 4 hr before digoxin
6	59M	65	Inf	812	43	1151	0.94	72	Morphine 24 mg, 5 to 10 hr before digoxin
7	65M	64	Ant	850	82	714	1.15	66	Metoclopramide 2, 7 and 12 hr after digoxin
8	72M	51	Inf	891	90	327	1.02	78	. . .
9	80M	70	Ant	429	30	203	1.20	101	Metoclopramide 5 hr after digoxin
10	79M	60	Ant	1277	143	919	0.95	54	. . .
11	56M	52	Ant	1105	*	344	1.02	120	Morphine 6 mg, 4 hr before, 24 mg after digoxin
12	41M	76	Ant	174	*	188	1.07	144	. . .
Control subjects									
Mean	60 (7M, 2F)	64	. . .	86	. . .	215	1.06	103	. . .
SEM	16	11	. . .	17	. . .	60	0.17	21	. . .

* Not analyzed.
Ant = anterior; CK = creatinine kinase; HBD = hydroxybutyric acid dehydrogenase; Inf = inferior; MB = MB creatinine kinase; SEM = standard error of the mean.

Design of study: An oral dose of 0.75 mg of digoxin (three tablets of Digoxin®, 0.25 mg, Orion, Helsinki) was given with 50 cc of water after the patients had fasted for at least 6 hours. Fasting was continued for at least 4 hours after drug intake. Venous blood samples were drawn before and after 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours after administration of the drug. Urine was collected during the 24 hours after drug administration. During the 4 hour fasting period 5 of 12 patients received morphine for relief of pain; other drugs used during the study are listed in Table I. Hemodynamic measurements were made before administration of digoxin in the patient group.

Analysis of digoxin levels: Serum levels of digoxin were estimated by radioimmunoassay.[5] The lower limit of sensitivity of the method was 0.08 ng/ml.

Pharmacokinetic analysis: Plasma concentration-time curves were constructed; the peak serum digoxin concentra-

TABLE II

Hemodynamic Data in 12 Patients With Acute Myocardial Infarction Before Digoxin

Case no.	Heart Rate (beats/min)	Blood Pressure (mm Hg)	Cardiac Output (liters/min)	PCWP (mm Hg)	Cardiomegaly (X-ray film)	Pulmonary Congestion*
1	100	190/110	6.5	15	No	1
2	85	120/80	5.7	30	Yes	3
3	75	110/85	4.3	12	No	0
4	70	135/95	7.0	27	Yes	2
5	85	140/80	5.7	13	No	0
6	90	130/95	6.5	16	Yes	1
7	60	90/60	4.3	18	No	2
8	75	130/90	6.0	24	Yes	3
9	60	120/80	5.5	15	Yes	1
10	100	160/90	†	†	No	1
11	70	130/90	4.2	15	No	1
12	65	125/100	7.0	14	Yes	0
Mean	74	132/88	5.7	18	. . .	. . .
SEM	15	24/12	1.1	6	. . .	. . .

* 0 = normal; 1 = venous congestion; 2 = interstitial edema; 3 = alveolar edema.
† Not analyzed.
PCWP = pulmonary capillary wedge pressure; SEM = standard error of the mean.

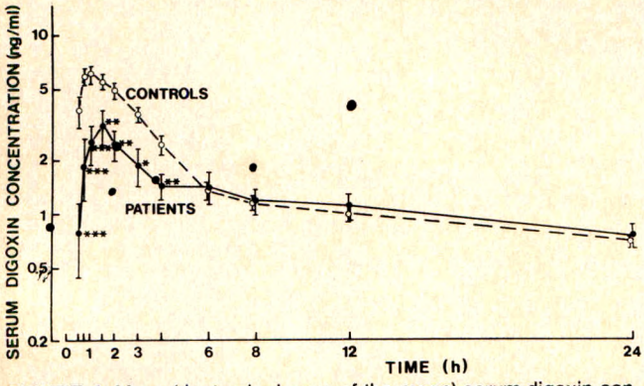

FIGURE 1. Mean (± standard error of the mean) serum digoxin concentration-time curves after a single oral dose of 0.75 mg. Patients with acute myocardial infarction are represented by **closed circles,** control subjects by **open circles.** * = P (probability) <0.05 compared with control subjects; ** = P <0.01 compared with control subjects; *** = P <0.001 compared with control subjects. h = hours.

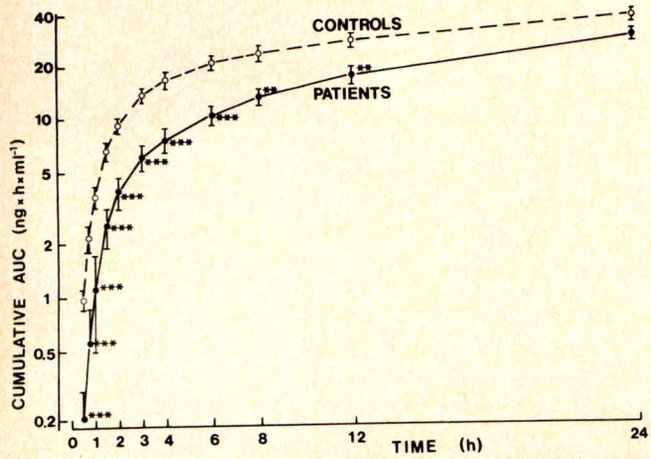

FIGURE 2. Mean (± standard error of the mean) areas under the serum digoxin concentration curve (AUC) after a single oral dose of 0.75 mg. The cumulative concentration curve of patients with acute myocardial infarction is represented by **solid line,** that of control subjects by a **broken line.** ** = P (probability) <0.01 compared with control subjects; *** = P <0.001 compared with control subjects. h = hours.

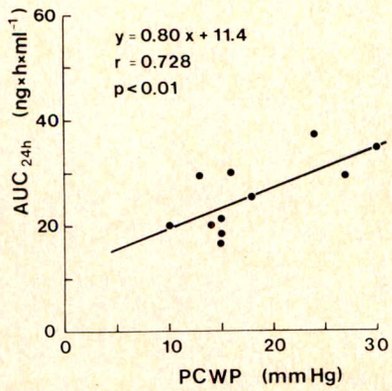

FIGURE 3. Relation between the area under the 24 hour serum digoxin concentration curve (AUC_{24h}) and the predigoxin mean pulmonary capillary wedge pressure (PCWP) in 11 patients with acute myocardial infarction. h = hour; p = probability; r = correlation coefficient.

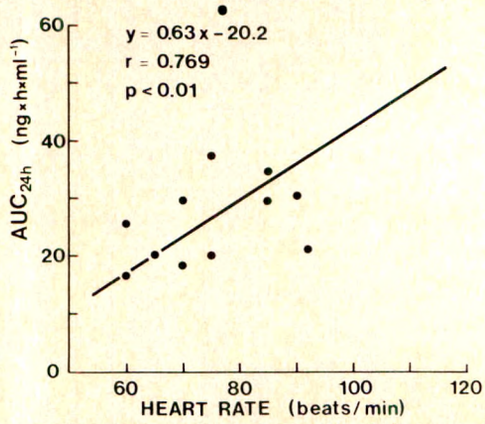

FIGURE 4. Relation between the area under the 24 hour serum digoxin concentration curve (AUC_{24h}) and the predigoxin heart rate in 12 patients with acute myocardial infarction. Abbreviations as in Figure 3.

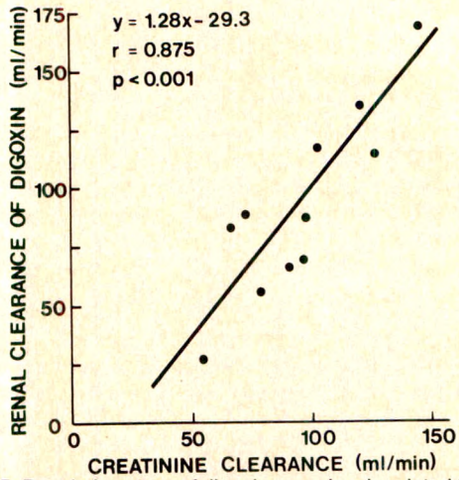

FIGURE 5. Renal clearance of digoxin was closely related to the creatinine clearance in 10 patients with acute myocardial infarction. Abbreviations as in Figure 3.

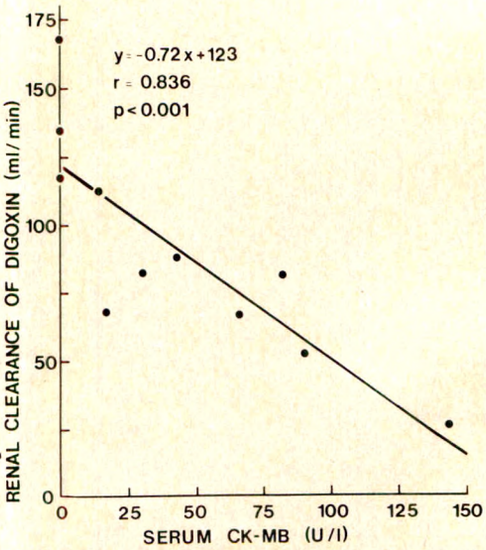

FIGURE 6. Renal clearance of digoxin diminished with increasing serum MB creatine kinase activity (CK-MB) in 11 patients with acute myocardial infarction. U/l = units per liter; other abbreviations as in Figure 3.

tion and its time were measured. The area under the digoxin serum concentration-time curve in the first 24 hours was determined by the trapezoidal rule. The renal clearance of digoxin was obtained by dividing the total amount of digoxin excreted in urine during 24 hours by the 24 hour area under the concentration curve.

Student's t *test* was used in comparing the results of patients and control subjects. Simple linear regressions were calculated to find out if there were correlations between pharmacokinetic and clinical measurements.

Results

Pharmacokinetics of digoxin: The serum digoxin concentration-time curves are shown in Figure 1. The concentrations of digoxin were significantly lower in patients than in control subjects up to 4 hours but thereafter the level was similar and declined at the same rate in both groups.

The cumulative area under the serum digoxin concentration-time curves was significantly lower ($P < 0.01$ or 0.001, Fig. 2) in patients than in control subjects up to 12 hours but thereafter the areas were similar in both groups (Table III).

The peak serum concentration of digoxin was significantly lower in patients (4.25 ± 0.59 ng/ml) than in control subjects (6.71 ± 0.41, $P < 0.001$, Table III). The mean time to reach the peak concentration was also longer. However, the difference was not statistically significant. The amount of digoxin excreted in urine and the renal clearance of digoxin did not differ between patients and control subjects (Table III). The peak serum concentration of digoxin in patients who had received morphine was significantly lower (2.8 ± 0.76 ng/ml) than in patients who had not received the drug (4.94 ± 0.53 ng/ml, $P < 0.001$). Also, the peak time tended to be longer in patients.

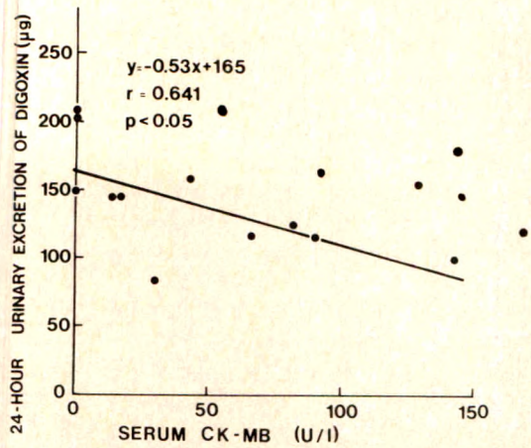

FIGURE 7. Relation between the 24 hour urinary excretion of digoxin and MB creatine kinase activity (CK-MB) in 11 patients with acute myocardial infarction. Abbreviations as in Figures 3 and 6.

Relations of pharmacokinetic and clinical measurements: The 24 hour area under the concentration curve revealed a significant positive correlation with pulmonary capillary wedge pressure and with heart rate (Fig. 3 and 4). The renal clearance of digoxin correlated positively to creatinine clearance ($P < 0.001$) (Fig. 5) and negatively to MB creatinine kinase activity ($P < 0.001$) (Fig. 6). The amount of digoxin excreted during 24 hours was negatively correlated with MB creatine kinase activity (Fig. 7). There was no significant correlation between the 24 hour area under the concentration curve and the amount of digoxin excreted during 24 hours in urine.

TABLE III

Pharmacokinetic Measurements Obtained After Oral Administration of Digoxin (0.75 mg) in 12 Patients With Acute Myocardial Infarction and in 9 Control Subjects

Case no.	C_{max} (µg/ml)	T_{max} (hours)	AUC_{24} (ng × hours × ml^{-1})	Renal Clearance (ml/min)	Recovery in Urine Over 24 Hours (µg)	Recovery in Urine Over 24 Hours (% of dose)
1	4.0	1.5	21.3	113	144	19.2
2	2.3	4.0	35.0	69	145	19.3
3	3.9	1.5	20.1			
4	5.2	1.0	29.6	117	208	27.7
5	5.3	3.0	29.3	67	118	15.7
6	4.2	6.0	30.1	88	159	21.2
7	6.4	1.5	25.6	82	126	16.8
8	4.6	1.5	37.2	52	117	15.6
9	2.7	2.0	16.8	83	84	11.2
10	7.4	0.75	64.3	27	103	13.7
11	1.0	12.0	18.5	135	149	19.9
12	4.0	2.0	20.0	168	202	26.9
Mean	4.3	3.1	29.0	91	141	18.8
SEM	0.5	0.9	3.7	12	12	1.5
Control subjects						
Mean	6.7	1.2	37.6	68	149	19.9
SEM	0.4	0.2	3.1	7	15	2.0
P	0.001	NS	NS	NS	NS	

AUC_{24} = area under serum digoxin concentration in the 24 hours after the dose; C_{max} = peak serum concentration; NS = not significant; *P* = probability; SEM = standard error of the mean; T_{max} = time of peak serum concentration.

Discussion

This clinical study demonstrates that there are clear changes in the pharmacokinetics of oral digoxin in patients with acute myocardial infarction complicated by left ventricular failure. Depression of left ventricular function is common in patients with acute transmural myocardial infarction. In our series this was manifested by elevation of the pulmonary capillary wedge pressure, pulmonary venous congestion on chest X-ray examination or by other clinical findings.

The gastrointestinal absorption of digoxin was delayed in our patients. The serum concentrations of digoxin up to 4 hours as well as peak concentrations were significantly lower and the peaks tended to occur later in patients than in control subjects. Moreover, the cumulative area under the serum digoxin concentration-time curve up to 12 hours was lower in patients than in control subjects.

Causes of delayed digoxin absorption: The delay of absorption of oral digoxin in acute myocardial infarction may be due to several factors.[1] Decreased gastrointestinal motility is one possible mechanism, particularly in the patients who received morphine.[6] Increased sympathetic activity is well documented in acute myocardial infarction and may also contribute to this mechanism.[7] Mesenteric blood flow may remain decreased in congestive heart failure, despite hemodynamic improvement obtained with digoxin.[8] Absorption of drugs is dependent on blood flow, as shown in animal experiments.[9] The vasoconstrictive action of digoxin may further decrease the mesenteric circulation.[10]

Equal amounts of digoxin were excreted in urine in both groups despite its delayed absorption. This finding indicates quantitatively equal absorption during the first 24 hours[11] as also evidenced by similar cumulative areas under the serum digoxin concentration-time curves during this period in both groups.

Correlation with left ventricular failure: The degree of left ventricular failure correlated in several ways with the kinetics of digoxin in the patient group. The 24 hour area under the concentration curve showed significant positive correlation with pulmonary capillary wedge pressure and with heart rate. Because the 24 hour area under the concentration curve did not correlate with the amount of digoxin excreted in urine during 24 hours, this finding may be due to a decreased volume of distribution of digoxin. Vasoconstriction and peripheral circulatory failure can reduce the rate and extent of uptake of drugs by peripheral tissues and thus decrease the apparent volume of distribution. This has been demonstrated with lidocaine, procainamide, disopyramide and mexiletine in acute myocardial infarction.[12]

Correlation with size of infarction: The size of myocardial damage estimated by the serum MB creatine kinase level was related to the decreased amount of digoxin excreted during 24 hours in urine. A large myocardial infarction is known to decrease the renal blood flow, with a consequent decrease of renal clearance of digoxin, which is the main route of elimination of digoxin.[13] Decreased excretion of digoxin in patients with a large infarction may contribute to the serum levels of digoxin from 12 to 24 hours in the patient group although the quantitative importance of this factor remains unclear.

Implications: Our results show that the total dosage of digoxin need not be modified in patients with acute myocardial infarction and left ventricular failure. Minor but clinically probably relevant changes were observed in the pharmacokinetics of a single oral dose. On the basis of the retarded absorption of oral digoxin a corresponding delay in the clinical response can be expected in patients with acute myocardial infarction complicated by left-sided cardiac failure.

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Hemodynamic Effects of Intravenous Metoprolol

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The hemodynamic effects of the cardioselective beta adrenergic blocking agent metoprolol, at a dose of 0.1 mg/kg body weight administered intravenously, were studied in 10 patients undergoing routine cardiac catheterization. The beta adrenergic blocking effect of the drug was confirmed by a highly significant reduction (53 percent, $P < 0.001$) in the mean heart rate response to a challenge with isoproterenol, and by a highly significant reduction (73 percent, $P < 0.001$) in the isoproterenol-induced increase in the first derivative of left ventricular pressure (dP/dt). An intrinsic negative inotropic effect was shown by a 43 percent reduction ($P < 0.05$) in the response of mean left ventricular dP/dt when the heart rate was fixed by atrial pacing alone. With the combination of atrial pacing and isoproterenol, metoprolol produced a 48 percent reduction ($P < 0.01$) in the response of mean left ventricular dP/dt, resulting from both the intrinsic depressor effect and the beta adrenergic blocking effect on the rate-independent beta agonist activity of isoproterenol.

There was no significant change in right atrial, femoral arterial or left ventricular end-diastolic pressure; analysis of left ventricular angiograms performed during atrial pacing before and after metoprolol revealed no significant effect on angiographic ejection fraction, pressure-volume loops or diastolic compliance. In two patients improvement in segmental wall motion was noted, and no deterioration was seen in any patient. Metoprolol is an effective cardioselective beta adrenergic blocking agent that, under these conditions, reduces catecholamine-induced increases in heart rate and left ventricular dP/dt without significant alteration in ejection fraction, preload or afterload.

Metoprolol is a cardioselective beta adrenergic blocking agent with no intrinsic agonistic activity.[1–3] When given orally it has been shown to reduce exercise-induced tachycardia in healthy volunteers,[4–11] to improve exercise tolerance in patients with angina[12] and to reduce blood pressure in hypertensive patients.[13,14] A similar effect on exercise-induced tachycardia has been shown with intravenous metoprolol[4–6,10] in healthy volunteers and in patients with coronary artery disease.[15] Stenberg et al.[5] and Aström and Johnsson[15] showed a small reduction in cardiac output at rest and after exercise. Sannerstedt and Wasir[16] studied the acute hemodynamic effects of intravenous metoprolol in hypertensive patients. Using a dose of 0.15 mg/kg of metopropol they reported significant decreases in heart rate, cardiac output and arterial blood pressure at rest and during exercise, without alteration of calculated stroke volume or systemic vascular resistance. Reale and Motolese[17] studied the effects of intravenous metoprolol (10 mg) in patients with coronary artery disease and showed significant changes in left ventricular dP/dt in addition to changes in cardiac output and heart rate.

Our study was designed to distinguish between the negative chronotropic and inotropic effects of intravenous metoprolol and between its

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intrinsic and beta adrenergic mediated negative inotropic effects. This was achieved by studying the hemodynamic response to an isoproterenol challenge, atrial pacing and a combination of atrial pacing and isoproterenol, using conventional hemodynamic measurements and left ventricular angiography before and after administration of the drug.

Methods

Study patients: Ten patients, 8 men and 2 women, aged 33 to 57 years (mean 50 years), were studied during routine cardiac catheterization, having given informed consent. All patients were being investigated for coronary artery disease and had presented with chest pain, and all except one were subsequently shown to have obstructive coronary artery disease on angiography. Patients with unstable or severe angina pectoris were excluded from the study.

Cardiac catheterization procedures: The patients were studied in the fasting state after premedication with 10 mg of diazepam. Administration of all cardioactive drugs had been stopped for at least 24 hours before the procedure. Left and right heart catheterization was performed from the brachial route using a Millar micromanometer angiographic catheter (PC 481) for left ventricular angiography and pressure recording, and a Zucker catheter (USCI) was inserted in the right atrium for pacing and pressure recordings.

Left ventricular pressure, its first differential (dP/dt) derived with an analog differentiator, right atrial pressure and femoral arterial pressure were recorded at rest and after the following interventions: (1) an intravenous bolus injection of isoproterenol sufficient to increase the heart rate at rest by at least 20 percent of its value (1 to 3 μg); (2) atrial pacing for 1 minute at a rate of 10 beats greater than the rate achieved with the isoproterenol challenge in (1); and (3) atrial pacing for 1 minute combined with the same isoproterenol challenge in (1), the pressures being recorded continuously after each isoproterenol challenge.

A left ventricular angiogram, in the 30° right anterior oblique position, was then obtained with the heart rate controlled by atrial pacing at the same rate used in interventions (2) and (3). Pressure was continuously recorded from the left ventricle during dye injection, and a cine exposure marker that was recorded simultaneously with the pressure allowed the derivation of the pressure-volume relations of the left ventricle.

Metoprolol, 0.1 mg/kg, was then administered intravenously over a period of 5 minutes, and after 15 minutes had elapsed, the pressure measurements and left ventricular angiogram were repeated in the same sequence as before administration of metoprolol. Finally, coronary arteriography was performed using the Sones technique.

Left ventricular angiograms and simultaneous left ventricular pressure measurements were analyzed to assess overall and regional changes in left ventricular performance using techniques previously described in this laboratory.[18,19] Diastolic compliance and pressure-volume loop efficiency were also calculated from the pressure-volume relations, using criteria previously described.[19] The inherent limitations of the analysis[18,19] were minimized with the use of comparisons of wall motion in each patient before and after drug intervention.

Results

Satisfactory recordings were obtained in all patients. Studies were incomplete in two patients: in Patient 3 because recordings were made of the response to isoproterenol alone after administration of metoprolol; and in Patient 6 because an unsatisfactory heart rate response (an 8 percent increase in heart rate) was obtained after isoproterenol challenge at rest, despite the maximal dose of 3 μg of isoproterenol allowed, and recordings were not made during atrial pacing alone after metoprolol had been administered.

Satisfactory left ventricular angiograms were obtained in all but one patient (Patient 9) in whom ventricular ectopic complexes during control angiography made the film unsuitable for accurate analysis. In Patient 3 atrial pacing failed during angiography. However, these angiograms were also analyzed because the sinus rate before and after metoprolol was similar. In Patient 1 the pacing rate after metoprolol was 10

TABLE I

Hemodynamic Data

Case	Heart Rate (beats/min)				Left Ventricular Pressure (dP/dt) (mm Hg·sec^{-1})								Pressures (mm Hg)					
	Rest		Increase (isoproterenol)		Rest		Increase (isoproterenol)		Increase (pacing)		Increase (pacing + isoproterenol)		RA Mean (paced)		RFA Mean (paced)		LVEDP	
no.	C	M	C	M	C	M	C	M	C	M	C	M	C	M	C	M	C	M
1	69	75	24	8	1225	1250	1600	500	1025	375	1525	1125	6	6	85	110	12	17
2	70	69	15	7	1750	1625	1125	250	500	250	1250	500	6	6	115	105	10	7
3	70	70	15	—	1100	1100	550	—	250	0	650	150	3	4	102	100	25	14
4	68	76	24	10	1600	1650	800	400	400	100	1250	450	0	0	95	90	10	10
5	68	68	28	16	2125	1750	3250	500	125	500	3250	1500	7	10	128	127	18	14
6	65	80	5	0	1900	1550	1300	350	550	—	1800	1800	7	2	180	120	27	14
7	75	71	17	7	1850	1500	1450	250	50	400	1150	650	3	4	125	120	10	15
8	51	46	16	11	1150	1100	550	50	500	250	1100	600	5	6	85	85	15	15
9	67	70	13	5	1550	1400	1550	250	600	200	2150	600	3	4	110	105	15	15
10	73	73	32	15	1750	1500	2000	850	750	350	1850	1100	1	2	95	105	5	5
Mean	67	70	18.9	8.8	1602	1442	1417	378	475	269	1587	847	4.1	4.4	112	107	13.8	13.2
SE	2	3	2.7	1.6	116	76	266	76	97	52	244	172	0.8	0.9	9.4	4.4	2.7	1.2
P	NS		<0.001		<0.05		<0.001		<0.05		<0.01		NS		NS		NS	

C = control; LVEDP = left ventricular end-diastolic pressure; M = metoprolol; NS = not significant; *P* = probability; RA = right atrial; RFA = right femoral artery; SE = standard error.

beats/min higher than before metoprolol because of a technical error.

Heart rate: The changes in heart rate and measured pressures are shown in Table I. The mean heart rate at rest was 68 ± 2 beats/min under control conditions and 70 ± 3 beats/min after metoprolol, but the change was not significant. The mean increase in heart rate with isoproterenol was 18.9 ± 2.7 beats/min before metoprolol but 8.8 ± 1.7 beats/min after the drug. This reduction (53 percent) in the heart rate response to an isoproterenol challenge is highly significant ($P < 0.001$).

Pressure analysis: Mean left ventricular dP/dt was 1,602 ± 116 mm Hg·sec^{-1} before metoprolol, and decreased to 1,442 ± 76 mm Hg·sec^{-1} after metoprolol, a reduction that was probably significant (10 percent, $P < 0.05$). The rise in left ventricular dP/dt after an isoproterenol challenge was 1,417 ± 266 mm Hg·sec^{-1} before, and 376 ± 76 mm Hg·sec^{-1} after metoprolol; this, like the heart rate response, was a highly significant reduction (73 percent, $P < 0.001$). Atrial pacing alone increased left ventricular dP/dt by 475 ± 97 mm Hg·sec^{-1} before, and 269 ± 52 mm Hg·sec^{-1} after metoprolol; this reduction after administration of the drug is also probably significant (43 percent, $P < 0.05$). The combination of atrial pacing and isoproterenol resulted in a mean rise of left ventricular dP/dt of 1,587 ± 244 mm Hg·sec^{-1} before and 847 ± 172 mm Hg·sec^{-1} after metoprolol, a significant reduction (48 percent, $P < 0.001$) in the response to the isoproterenol challenge when heart rate was fixed. Before metoprolol, the increase in left ventricular dP/dt with the combination of isoproterenol and atrial pacing (1,587 ± 244 mm Hg·sec^{-1}) was not significantly different from the increase with isoproterenol alone (1,417 ± 266 mm Hg·sec^{-1}).

There was no significant change after metoprolol in mean right atrial or femoral arterial pressures during atrial pacing with the heart rate fixed, although in Patient 6 right femoral arterial pressure decreased greatly from 250/136 to 180/90 mm Hg after the drug. Left ventricular end-diastolic pressure decreased in some patients and increased slightly in others, but there was no overall change.

Angiographic analysis: The data derived from the left ventricular angiograms are shown in Table II. For the total group there was no significant change in ejection fraction determined by analysis of end-systolic and end-diastolic frames before and after metoprolol. Patient 1, whose heart rate after metoprolol was 10 beats/min higher than before metoprolol, had a 10 percent increase in ejection fraction, and Patients 6 and 8 each had a 5 percent increase; Patient 10 had a 5 percent decrease.

Estimations of cardiac output derived from the angiographic analysis revealed only minor changes after metoprolol, the mean cardiac output being unchanged at 5.2 ± 0.7 liters·min^{-1}. There were variable changes in the calculated systemic vascular resistance but no significant difference in the mean values before and after metoprolol, which were 24 ± 3 units and 23 ± 3 units, respectively.

Analysis of the pressure-volume loops showed a slight shift to the right in two patients (Patients 2 and 4; Fig. 1, left), reflecting an equal increase in diastolic and systolic volumes and a slight shift to the left in four patients (Patients 1, 3, 6 and 8; Fig. 1, right), reflecting a slight decrease in volumes. No major change was observed in any patient. The efficiency of the cardiac cycle calculated from the pressure-volume loops also showed variable changes with a mean of 78 ± 2 percent after metoprolol that was not significantly altered from the mean of 81 ± 2.8 percent before metoprolol. Compliance calculated from diastolic pressure-volume relations[19] was extremely variable, and there was no significant difference in the mean values before and after metoprolol (0.028 ± 0.011 and 0.014 ± 0.006, respectively).

TABLE II

Angiographic Analysis

Case no.	End-Systolic Volume (ml)		End-Diastolic Volume (ml)		Stroke Volume (ml)		Ejection Fraction (%)		Heart Rate (beats/min)		Cardiac Output (liters·min^{-1})		Systemic Vascular Resistance (units)		Efficiency (%)		Diastolic Compliance (K)	
	C	M	C	M	C	M	C	M	C	M	C	M	C	M	C	M	C	M
1	53	34	107	84	54	50	50	60	100	110	5.4	5.5	15	19	94	78	0.006	0.007
2	45	48	116	120	61	72	61	60	100	100	6.1	7.2	18	14	82	75	0.082	0.057
3	63	56	120	104	57	48	49	47	62	58	3.5	2.8	28	35	66	68	0.010	0.011
4	58	65	92	98	34	33	37	37	102	102	3.5	3.4	27	26	82	73	0.019	0.009
5	42	54	117	129	75	75	70	68	115	115	8.6	8.3	14	14	85	88	0.008	0.009
6	49	40	96	92	47	52	51	56	103	103	4.9	5.3	35	22	81	85	0.009	0.002
7	29	29	67	70	38	41	57	58	102	102	3.9	4.2	32	28	85	76	0.011	0.008
8	52	37	152	130	100	93	66	71	80	80	8.0	7.4	10	11	70	79	0.009	0.004
9	Not analyzed																	
10	32	35	59	62	27	27	48	43	100	100	2.7	1.7	35	39	87	75	0.095	0.026
Mean	47	44	103	98	55	55	54	56	96	97	5.2	5.2	24	23	81	78	0.028	0.014
SE	2.8	4.0	9.5	8.2	7.5	7.1	3.4	3.7	5.2	5.8	0.7	0.7	3	3	2.8	2.0	0.011	0.006

C = control; M = metoprolol; SE = standard error.

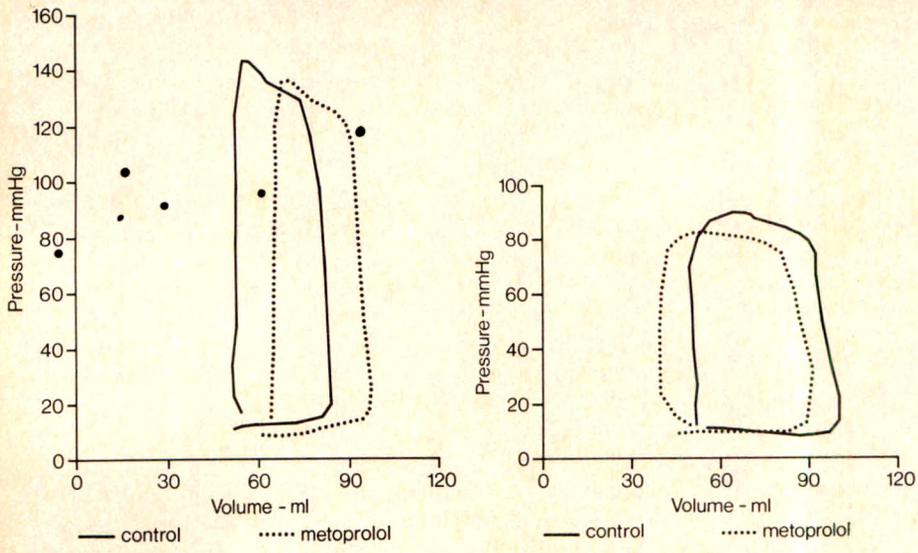

FIGURE 1. Pressure-volume loops. **Left,** in Patient 4, showing a slight increase in systolic and diastolic volumes after metoprolol. **Right,** in Patient 6, showing a slight decrease in systolic and diastolic volumes after metoprolol.

Analysis of segmental wall motion indicated slight improvement in anterior wall movement in two patients (Patients 1 and 8; Fig. 2, left) and no definite alteration in the other seven patients in whom angiographic analysis was possible (Fig. 2, right).

Discussion

In this study the beta adrenergic blocking effect of intravenous metoprolol was confirmed by a marked reduction (53 percent, $P < 0.001$) in the heart rate response to an isoproterenol challenge and by a significant decrease (48 percent, $P < 0.01$) in the change of left ventricular dP/dt with the combination of atrial pacing and isoproterenol, which eliminates the effect of changes in heart rate on left ventricular dP/dt.

Effect on heart rate: The mean heart rate at rest was not significantly altered by intravenous metoprolol in the dosage used (0.1 mg/kg). Other investigators[4–6,10,15–17] who demonstrated a reduction in heart rate at rest with intravenous metoprolol used larger doses. However, there was a reduction by 10 percent in the mean left ventricular dP/dt at rest after metoprolol. This decrease was due in part to its intrinsic depressor effect (negative inotropic effect independent of beta antagonist activity), and in part to its beta adrenergic blocking action on sympathetic tone at rest. It is likely that the intrinsic depressor effect was dominant under these conditions because the heart rate was unchanged.

The intrinsic depressor effect of metoprolol: This effect can also be estimated from the changes in left ventricular dP/dt with pacing before and after metoprolol. If it is assumed that sympathetic tone at rest is unaltered with atrial pacing at the rates used in this study, and that it remains constant after metoprolol, the reduction by metoprolol of the mean rise in left ventricular dP/dt with pacing reflects its intrinsic depressor activity. This reduction of 206 mm Hg·sec^{-1}, from a mean of 475 mm Hg·sec^{-1} to a mean of 269 mm Hg·sec^{-1}, was 43 percent of the increase in left ventricular dP/dt (475 mm Hg·sec^{-1}) with pacing before metoprolol ($P < 0.05$).

The difference between the mean rise in left ventricular dP/dt with the combination of isoproterenol and pacing and with pacing alone is a measure of the rate-independent beta-agonist effect of isoproterenol. This difference of 1,112 mm Hg·sec^{-1} (1,587 mm Hg·sec^{-1} − 475 mm Hg·sec^{-1}) was reduced by metoprolol to 578 mm Hg·sec^{-1} (847 mm Hg·sec^{-1} − 269 mm Hg·sec^{-1}). The reduction of 534 mm Hg·sec^{-1} therefore reflects the rate-independent beta adrenergic blocking effect of metoprolol under these conditions. This result is 72 percent of the total reduction in left ventricular dP/dt response (740 mm Hg·sec^{-1}), the intrinsic depressor activity of metoprolol accounting for 28 percent (206 mm Hg·sec^{-1}) of the total reduction.

Role of heart rate in assessment of effect on dP/dt: Measurement of the effect of an increase in heart rate on left ventricular dP/dt showed it to be potent. When the heart rate was fixed by atrial pacing at a level just above that obtained with isoproterenol, metoprolol reduced the mean rise in left ventricular dP/dt caused by the combination of pacing and isoproterenol from 1,587 mm Hg·sec^{-1} to 847 mm Hg·sec^{-1}, a reduction of 47 percent. This is in marked contrast to the effects of metoprolol when the heart rate is uncontrolled, the reduction in the mean response of left ventricular dP/dt to isoproterenol alone being from 1,417 to 378 mm Hg·sec^{-1} (73 percent). These results underline the importance of the often ignored influence of heart rate when assessing the effects of this type of drug on left ventricular dP/dt as an index of left ventricular function.

Effect on cardiac output: Previous studies showed a slight decrease in cardiac output with intravenous metoprolol,[5,15–17] but this was associated with a reduction in heart rate and little or no change in stroke volume. Our study was designed to eliminate the negative chronotropic effect of beta adrenergic blockade on cardiac output by using atrial pacing during left ventricular angiography. The lack of any significant

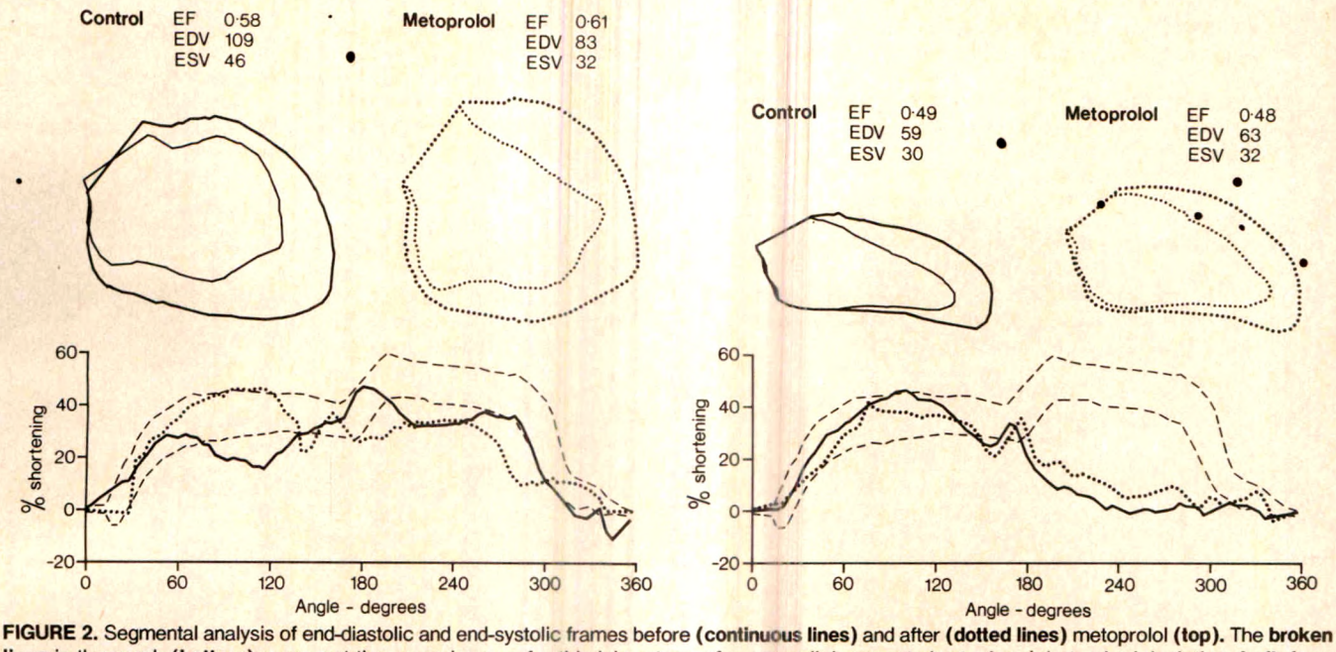

FIGURE 2. Segmental analysis of end-diastolic and end-systolic frames before **(continuous lines)** and after **(dotted lines)** metoprolol **(top).** The **broken lines** in the graph **(bottom)** represent the normal range, for this laboratory, of mean radial percent shortening ±1 standard deviation. **Left,** from Patient 1, showing anterior wall dyskinesia (70° to 130°), which is lessened after metoprolol. **Right,** from Patient 10, showing marked inferior wall dyskinesia (180° to 300°), not significantly altered by metoprolol. EDV = end-diastolic volume (ml); EF = ejection fraction; ESV = end-systolic volume (ml).

alteration in cardiac output after metoprolol reflects this aspect of the study design. However, it is possible that with a larger dose of metoprolol a greater negative inotropic effect might result in a reduction in cardiac output even when heart rate is maintained by atrial pacing.

Effect on systemic vascular resistance: The absence of any statistically significant rise in systemic vascular resistance in our study is in agreement with the findings of most other investigators[15–17] who have used intravenous metoprolol, although Stenberg et al.[5] found a small but significant increase at rest and a tendency to increase during exercise after a dose of 0.15 mg/kg of metoprolol, 50 percent greater than the dose used in this study. An unchanged systemic vascular resistance would be expected with a cardioselective beta adrenergic blocking agent, in contrast to the increase in systemic vascular resistance that is seen with a nonselective beta adrenergic blocking agent such as propranolol, probably as a result of the latter's blockade of vascular beta$_2$-adrenoceptors with an ensuing relative preponderance of alpha adrenoceptor activity.[20]

Effect on segmental wall motion: A possible explanation for the improvement in anterior wall movement in Patients 1 and 8 is that the metoprolol-induced reduction in left ventricular dP/dt resulted in an improvement in the ratio of oxygen supply and demand in areas of myocardium that may have been ischemic at the atrial pacing rate used. The changes in Patient 1 (Fig. 2A) were not likely to be due to the slightly increased heart rate after metoprolol because this increased rate would be expected to have a deleterious rather than beneficial effect on the function of the ischemic myocardium. Similar changes were observed in Patient 8 whose heart rate was the same before and after metoprolol. Improvement in the ratio of oxygen supply and demand might also account for the maintenance of ejection fraction and cardiac output in the presence of a reduction in left ventricular dP/dt, although it is also possible that the techniques used in this study were not sensitive enough to detect a small decrease in ejection fraction and cardiac output.

Implications: Metoprolol is an effective cardioselective beta adrenergic blocking agent which under these conditions reduces catecholamine-induced tachycardia and left ventricular dP/dt without significant alteration in preload or afterload ejection fraction. Analysis of segmental wall motion before and after metoprolol reveals only minor beneficial changes in a small proportion of patients with coronary artery disease, and assessment of pressure-volume relations reveals no significant alteration in synchronicity or mechanical efficiency of the left ventricle. In clinical use with this dose the main cardiac depressant action will result from the blockade of increased sympathetic activity.

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PROBLEM:

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*Patent Pending

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Dobutrex is a potent, positive inotropic agent whose primary activity results from stimulation of the β receptors of the myocardial muscle cells.[1]

Hemodynamic Improvements

Dobutrex has minimum effect on the adrenergic receptors in the vasculature.[1] In most patients, blood pressure changes are small, and decreases in afterload and preload have been reported in clinical investigations (see warnings).[2]

Small Effect on Heart Rate and Automaticity

Dobutrex has minimum effect on ventricular automaticity[3] and does not reduce blood pressure.[4] This, together with its low chronotropic potential, reduces the risk of arrhythmia (see warnings).

Renal Output and Urine Flow

Dobutrex does not have the direct renal vasodilative effect of low-dose dopamine; however, in patients with heart failure, Dobutrex generally promotes a diuresis as renal perfusion rises with the increased cardiac output.[5]

Direct-Acting

Unlike dopamine, Dobutrex acts directly on the myocardium and does not depend on the release of endogenous norepinephrine for its inotropic activity.

Myocardial Oxygen Balance

Increases in coronary heart perfusion due to increased cardiac output, together with a favorable influence on some of the major determinants of oxygen consumption (for example, decreases in left-ventricular filling pressure, decreases in systemic vascular resistance, and a mild chronotropic effect [2,6]), suggest that Dobutrex improves or maintains myocardial oxygen balance.

Infrequent Side Effects

Increases in heart rate, blood pressure, and ventricular ectopic activity have occurred. The drug is contraindicated in patients with idiopathic hypertrophic subaortic stenosis. In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used before therapy with Dobutrex is instituted. For warnings, precautions, and adverse reactions, see the brief summary of prescribing information.

Because of the rapid onset and brief duration of action of Dobutrex, precise adjustment of cardiac stimulation is possible by regulation of the rate of administration. As a result, when undesirable effects arise, temporary discontinuation of the infusion or reduction in dosage will generally reverse the adverse conditions. No additional remedial measures are usually necessary.

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Brief Summary
Consult the package literature for prescribing information.

Indications and Usage: Dobutrex® (dobutamine hydrochloride, Lilly) is indicated when parenteral therapy is necessary for inotropic support in the short-term treatment of adults with cardiac decompensation due to depressed contractility resulting either from organic heart disease or from cardiac surgical procedures.

In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to instituting therapy with Dobutrex.

Contraindication: Dobutrex is contraindicated in patients with idiopathic hypertrophic subaortic stenosis.

Warnings: 1. *Increase in Heart Rate or Blood Pressure*—Dobutrex may cause a marked increase in heart rate or blood pressure, especially systolic pressure. Approximately 10 percent of patients in clinical studies have had rate increases of 30 beats/minute or more, and about 7.5 percent have had a 50-mm Hg or greater increase in systolic pressure. Reduction of dosage usually reverses these effects promptly. Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation are at risk of developing rapid ventricular response. Patients with preexisting hypertension appear to face an increased risk of developing an exaggerated pressor response.

2. *Ectopic Activity*—Dobutrex may precipitate or exacerbate ventricular ectopic activity, but it rarely has caused ventricular tachycardia.

Precautions: 1. **During the administration of Dobutrex, as with any adrenergic agent, ECG and blood pressure should be continuously monitored. In addition, pulmonary wedge pressure and cardiac output should be monitored whenever possible to aid in the safe and effective infusion of Dobutrex.**

2. Hypovolemia should be corrected with suitable volume expanders before treatment with Dobutrex is instituted.

3. Animal studies indicate that Dobutrex may be ineffective if the patient has recently received a beta-blocking drug. In such a case, the peripheral vascular resistance may increase.

4. No improvement may be observed in the presence of marked mechanical obstruction, such as severe valvular aortic stenosis.

Usage Following Acute Myocardial Infarction—Clinical experience with Dobutrex following myocardial infarction has been insufficient to establish the safety of the drug for this use. There is concern that any agent which increases contractile force and heart rate may increase the size of an infarction by intensifying ischemia, but it is not known whether dobutamine does so.

Usage in Pregnancy—Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility, harm to the fetus, or teratogenic effects due to dobutamine. However, the drug has not been administered to pregnant women and should be used only when the expected benefits clearly outweigh the potential risks to the fetus.

Pediatric Use—The safety and effectiveness of Dobutrex for use in children have not been studied.

Drug Interactions—There was no evidence of drug interactions in clinical studies in which Dobutrex was administered concurrently with other drugs, including digitalis preparations, furosemide, spironolactone, lidocaine, glyceryl trinitrate, isosorbide dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid, and acetaminophen. Preliminary studies indicate that the concomitant use of dobutamine and nitroprusside results in a higher cardiac output and, usually, a lower pulmonary wedge pressure than when either drug is used alone.

Adverse Reactions: *Increased Heart Rate, Blood Pressure, and Ventricular Ectopic Activity*—A 10 to 20-mm increase in systolic blood pressure and an increase in heart rate of five to 15 beats per minute have been noted in most patients. (See Warnings regarding exaggerated chronotropic and pressor effects.) Approximately 5 percent of patients have had increased premature ventricular beats during infusions. These effects are dose related.

Miscellaneous Uncommon Effects—The following adverse effects have been reported in 1 to 3 percent of patients: nausea, headache, anginal pain, nonspecific chest pain, palpitations, and shortness of breath.

No abnormal laboratory values attributable to Dobutrex have been observed.

Longer-Term Safety—Infusions of up to 72 hours have revealed no adverse effects other than those seen with shorter infusions.

Overdosage: In case of overdosage, as evidenced by excessive alteration of blood pressure or by tachycardia, reduce the rate of administration or temporarily discontinue Dobutrex until the patient's condition stabilizes. Because the duration of action of Dobutrex is short, usually no additional remedial measures are necessary.

Administration and Dosage: *Reconstitution and Stability*—Dobutrex® (dobutamine hydrochloride, Lilly) is incompatible with alkaline solutions and should not be mixed with products such as 5% Sodium Bicarbonate Injection.

Dobutrex may be reconstituted with Sterile Water for Injection or 5% Dextrose Injection. To reconstitute, add 10 ml of diluent to Vial No. 7051 Dobutrex, 250 mg. If the material is not completely dissolved, add an additional 10 ml of diluent. The reconstituted solution may be stored under refrigeration for 48 hours or at room temperature for six hours.

Reconstituted Dobutrex must be further diluted to at least 50 ml prior to administration in 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Sodium Lactate Injection. Intravenous solutions should be used within 24 hours.

Solutions containing Dobutrex may exhibit a color that, if present, will increase with time. This color change is due to slight oxidation of the drug, but there is no significant loss of potency during the reconstituted time periods stated above.

Recommended Dosage—The rate of infusion needed to increase cardiac output usually ranges from 2.5 to 10 mcg/kg/min (see table). On rare occasions, infusion rates up to 40 mcg/kg/min have been required to obtain the desired effect.

Rates of Infusion for Concentrations of 250, 500, and 1000 mcg/ml

Drug Delivery Rate (mcg/kg/min)	Infusion Delivery Rate 250 mcg/ml* (ml/kg/min)	500 mcg/ml† (ml/kg/min)	1000 mcg/ml‡ (ml/kg/min)
2.5	0.01	0.005	0.0025
5	0.02	0.01	0.005
7.5	0.03	0.015	0.0075
10	0.04	0.02	0.01
12.5	0.05	0.025	0.0125
15	0.06	0.03	0.015

*250 mg per liter of diluent
†500 mg per liter or 250 mg per 500 ml of diluent •
‡1000 mg per liter or 250 mg per 250 ml of diluent

The rate of administration and the duration of therapy should be adjusted according to the patient's response, as determined by heart rate, presence of ectopic activity, blood pressure, urine flow, and, whenever possible, measurement of central venous or pulmonary wedge pressure and cardiac output.

Concentrations up to 5000 mcg/ml have been administered to humans (250 mg/50 ml). The final volume administered should be determined by the fluid requirements of the patient. • [081678]

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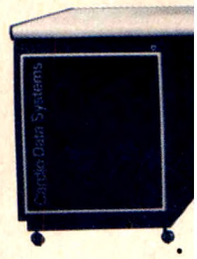

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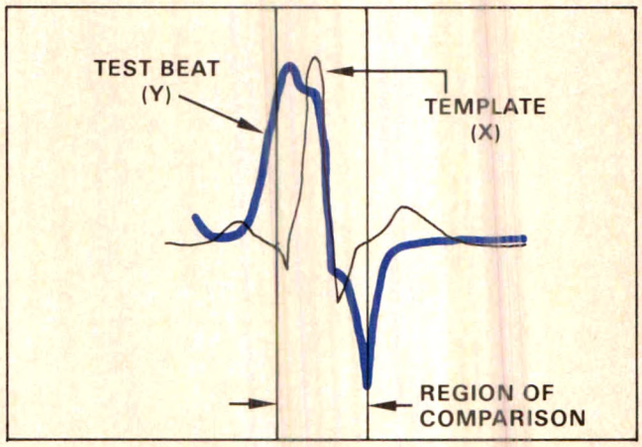

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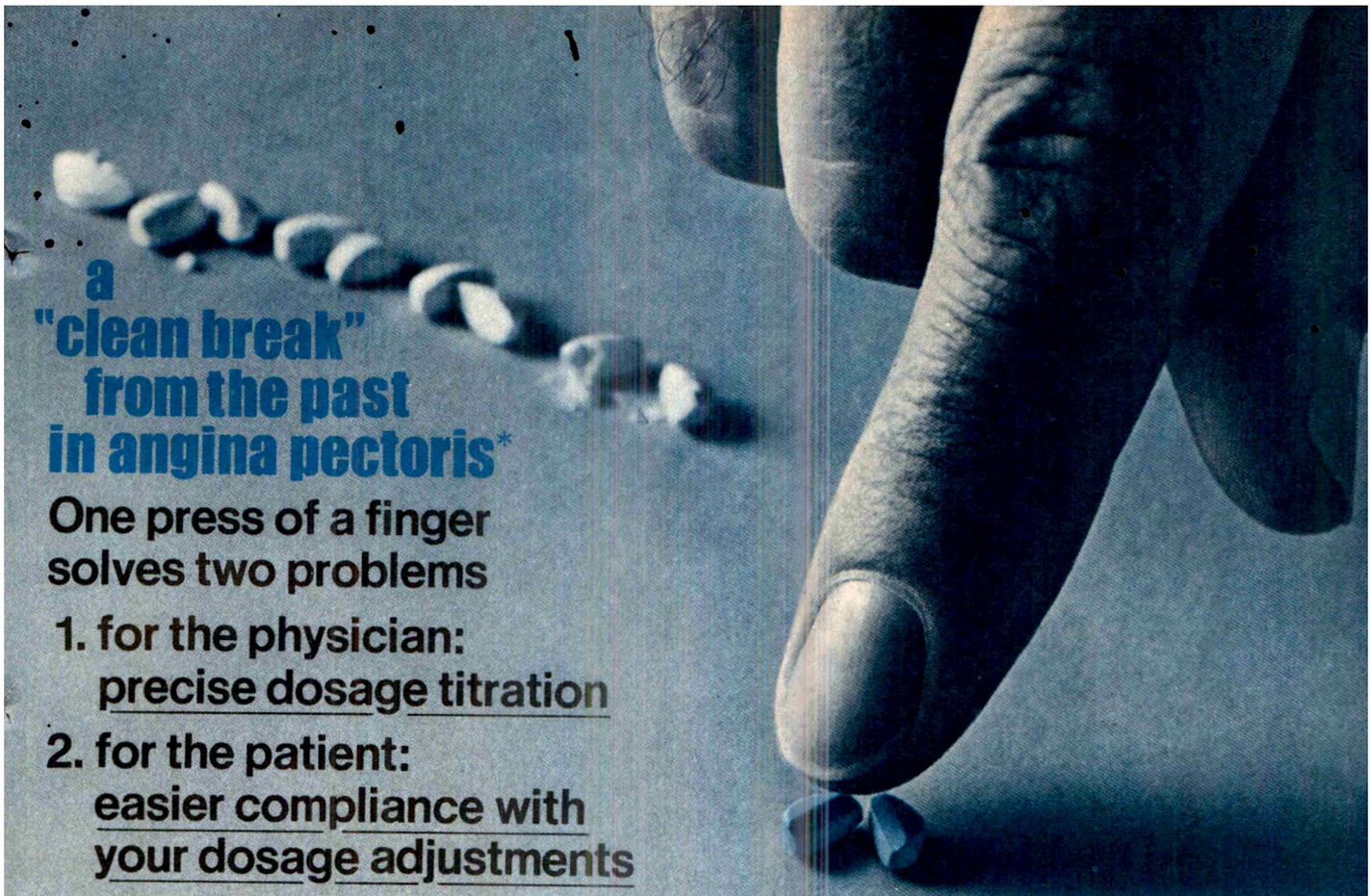

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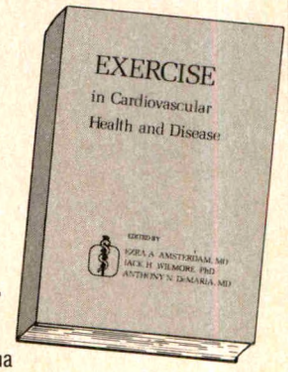

Edited by
Ezra A. Amsterdam, MD, Chief Coronary Care Unit, Univ. of Calif. School of Medicine
Jack H. Wilmore, PhD, Professor and Head Dept. of Physical Education & Athletics, Univ. Arizona
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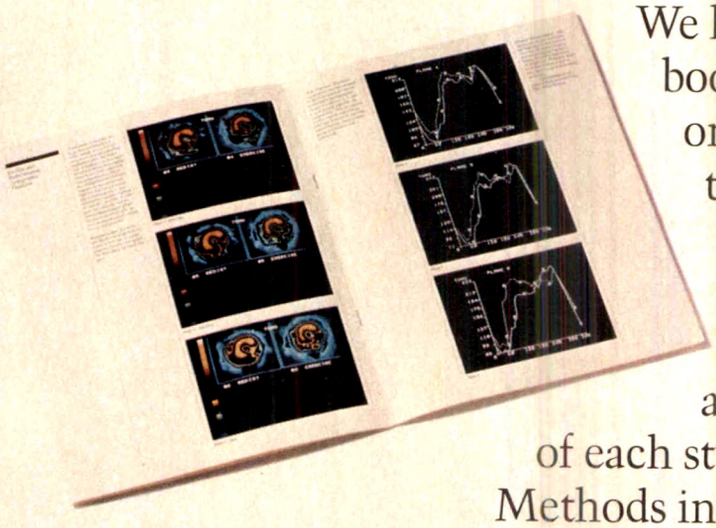

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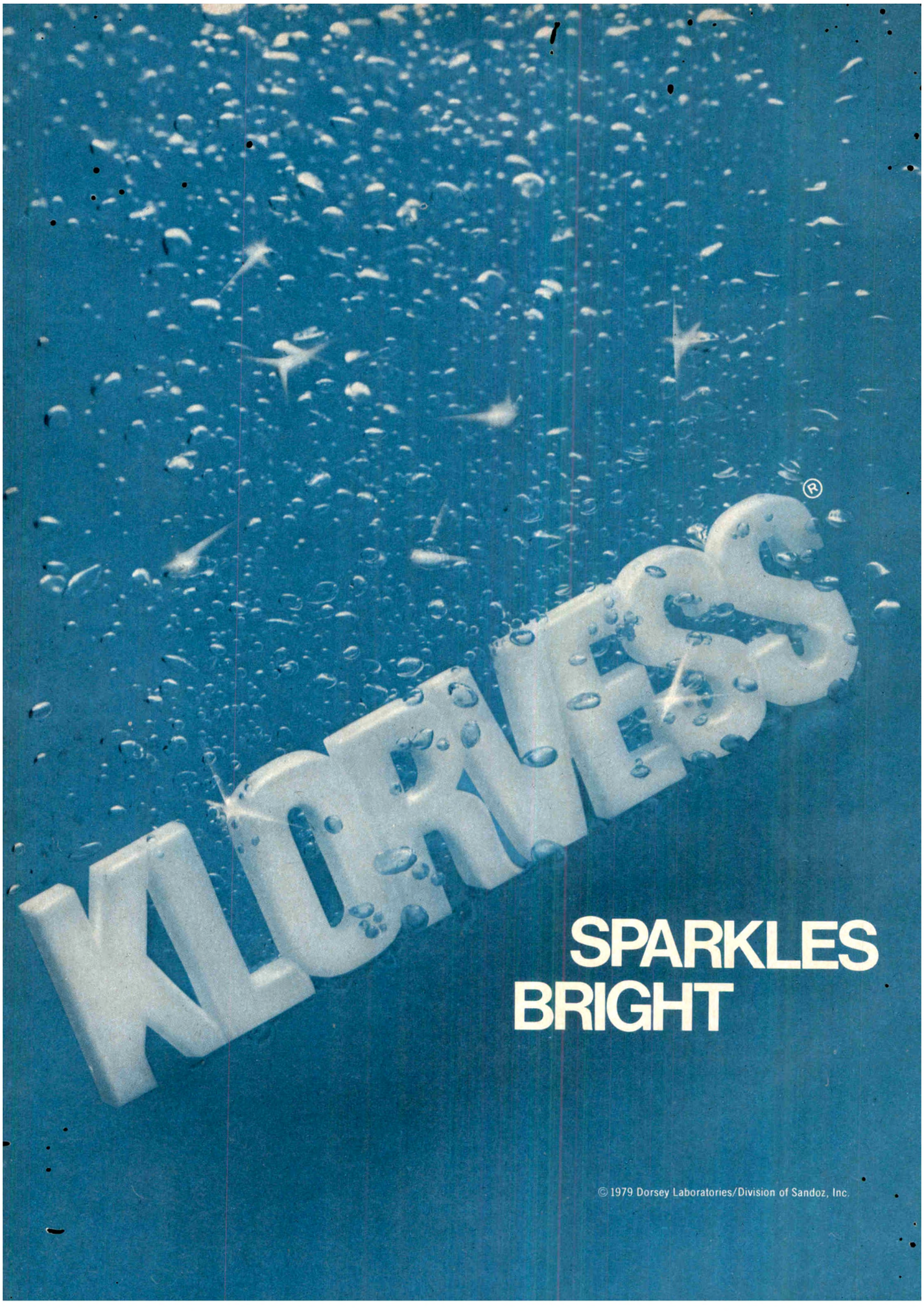
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CONTRAINDICATIONS: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

PRECAUTIONS: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements. Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis. High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest. To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve the packet contents of *Klorvess Effervescent Granules* in 3 to 4 ounces of cold water, fruit juice or other liquid or dilute each tablespoonful of *Klorvess (potassium chloride) 10% Liquid* in 3 to 4 ounces of cold water. Both of these solutions should be ingested slowly with or immediately after meals.

ADVERSE REACTIONS: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts. The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest. The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

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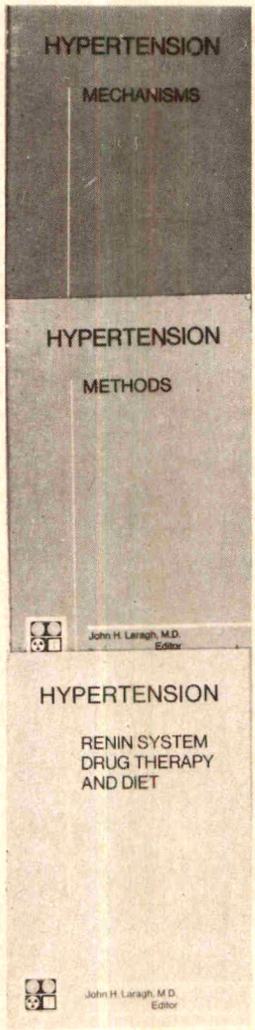

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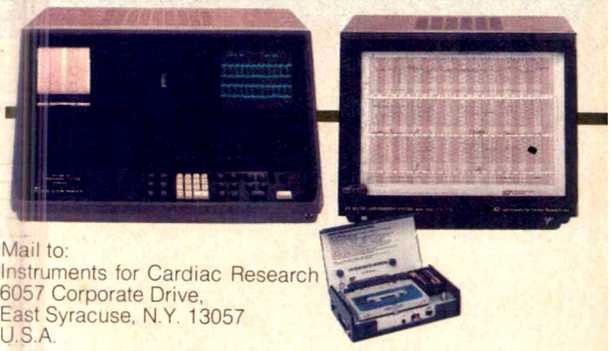

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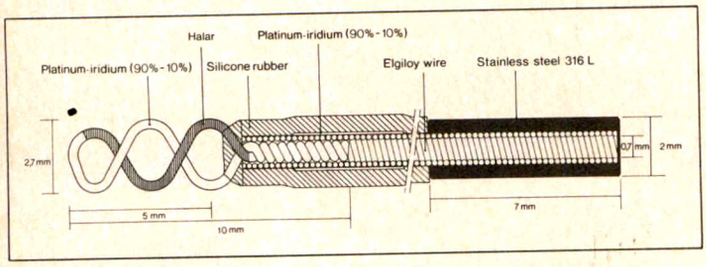

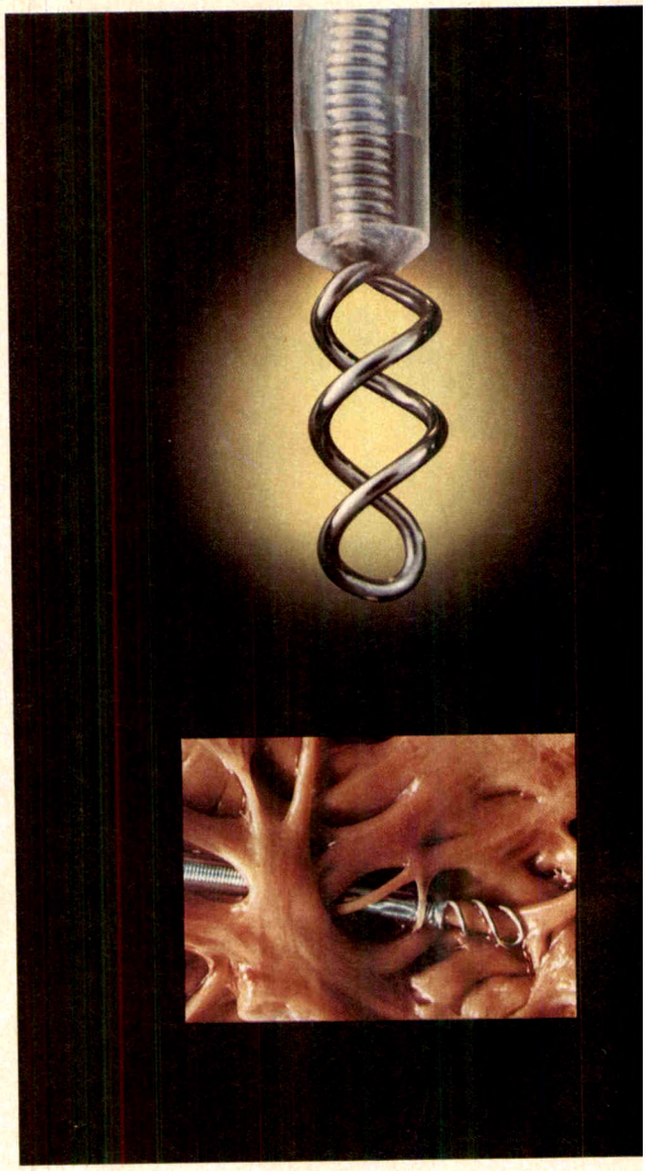

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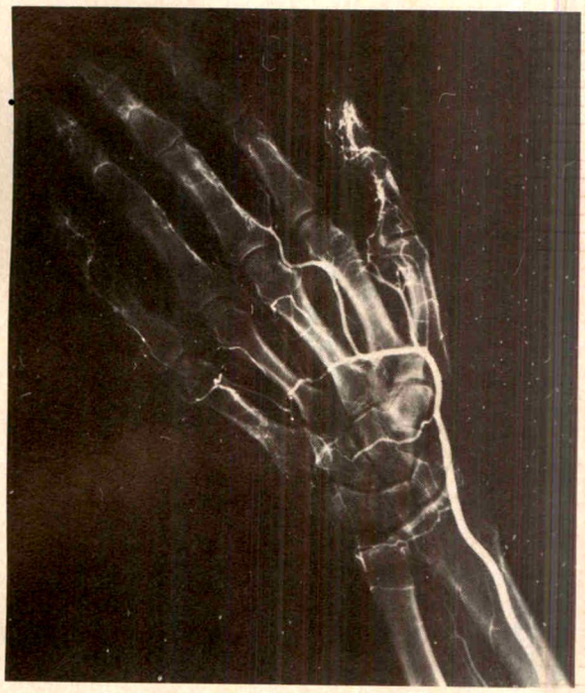

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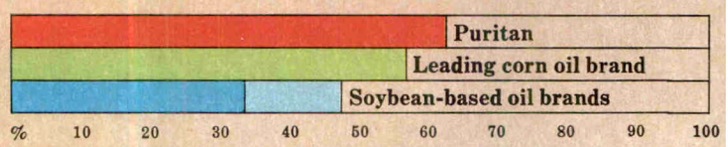

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Reference: 1. Witchi, J.C. et al., *J. Am. Dietetic Assoc. 72:* 384, 1978.

Selective Coronary Arteriography in Congenitally Corrected Transposition of the Great Arteries

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Three cases of congenitally corrected transposition of the great arteries in adults who underwent selective coronary arteriography are presented. The morphologic features of the epicardial coronary anatomy are distinctive and are identifiable angiographically as morphologically right and left coronary arteries that are specifically concordant with the morphologically right and left ventricles. This relation is constant in the presented cases, in previously published coronary arteriograms of congenitally corrected transposition of the great arteries and in a review of the anatomic studies of congenitally corrected transposition of the great arteries that identify the coronary arterial pattern. Thus the angiographic characteristics of the epicardial coronary arterial pattern permit identification of the morphologic features of the underlying ventricle regardless of other spatial relations.

The morphologic features of congenitally corrected transposition of the great arteries have been described in detail by Anderson et al.[1] and Allwork et al.[2] Although the coronary arterial pattern has been described in a few series of autopsies, only four cases of selective coronary arteriograms in patients with congenitally corrected transposition of the great arteries have been published.[3–6] Because of past misunderstanding of the morphologic features of the epicardial coronary arterial pattern in congenitally corrected transposition, prior descriptions of the coronary arteriograms in some of these patients have been misleading. We recently obtained selective coronary arteriograms from three patients with congenitally corrected transposition of the great arteries. These cases are presented in an attempt to clarify the terminology used to describe the epicardial coronary anatomy and to demonstrate further the usefulness of selective coronary arteriography in evaluating complex congenital heart disease.

Case Histories

Case 1: An asymptomatic 33 year old woman had an unexplained murmur since childhood. On physical examination a holosystolic grade 5/6 apical murmur was heard radiating to both sides of the sternum and to the axilla. A Q wave was present in lead V_1 of the electrocardiogram, and a straightened left heart border, retrosternal fullness and a left-sided stomach bubble were seen in chest X-ray films. Cardiac catheterization demonstrated congenitally corrected transposition of the great arteries with systemic atrioventricular (A-V) valve regurgitation. With use of the segmental designation suggested by Van Praagh,[7] a diagnosis of transposition of the great arteries {S, L, L} with systemic A-V valve regurgitation was made. The patient's coronary arteriograms are shown in Figure 1.

Case 2: An asymptomatic 27 year old woman had a cardiac murmur since childhood. Physical examination revealed the point of maximal cardiac impulse to be in the right side of the chest with a diffuse thrill. A grade 5/6 harsh systolic murmur was heard throughout the precordium. The electrocardiogram revealed complete heart block with marked right axis deviation and a prominent Q wave

From the Cardiology Branch, Department of Internal Medicine, Naval Regional Medical Center, San Diego, California; the National Naval Medical Center, Bethesda, Maryland; the Department of Pathology, Children's Hospital Medical Center and the Department of Pathology, Harvard Medical School, Boston, Massachusetts. This work was supported in part by Grants HLB 5855 and HLB 10436 from the National Institutes of Health, Bethesda, Maryland and by the Bureau of Medicine and Surgery Clinical Investigation Program, San Diego, California. Manuscript received March 14, 1979; revised manuscript received May 24, 1979, accepted May 30, 1979.

The opinions or assertions contained herein are those of the authors and are not to be construed as official or as a reflection of the views of the Department of the Navy.

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in lead V_1. In the chest X-ray film the cardiac apex was oriented to the right of the mid line; the stomach bubble was on the left side. A left-sided aortic arch and retrosternal fullness were present. Cardiac catheterization documented congenitally corrected transposition of the great arteries with a ventricular septal defect and pulmonary stenosis. The segmental designation was transposition of the great arteries {S, L, L}, ventricular septal defect, pulmonary stenosis and dextrocardia. The patient's coronary arteriograms are illustrated in Figure 2.

Case 3: An asymptomatic 25 year old male Navy pilot on active duty was found on routine physical examination to have an abnormal Q wave in lead V_1 of the electrocardiogram. No cardiac murmur was heard. The cardiac apex and stomach bubble were on the left side. Cardiac catheterization was required to preserve the patient's status as a pilot. Congenitally corrected transposition of the great arteries without cardiac defects was demonstrated. The segmental designation was transposition of the great arteries {S, L, L}. The coronary arteriograms revealed a left-sided vessel having large marginal branches and giving off the A-V nodal artery and posterior descending artery, consistent with a morphologically right coronary artery. The right-sided vessel gave off an anterior descending branch with septal perforating branches and a small circumflex branch, consistent with a morphologically left coronary artery.

Discussion

The three cases presented have congenitally corrected transposition of the great arteries defined as atrioventricular (A-V) discordance and transposition, that is, the morphologically right atrium drains into the mor-

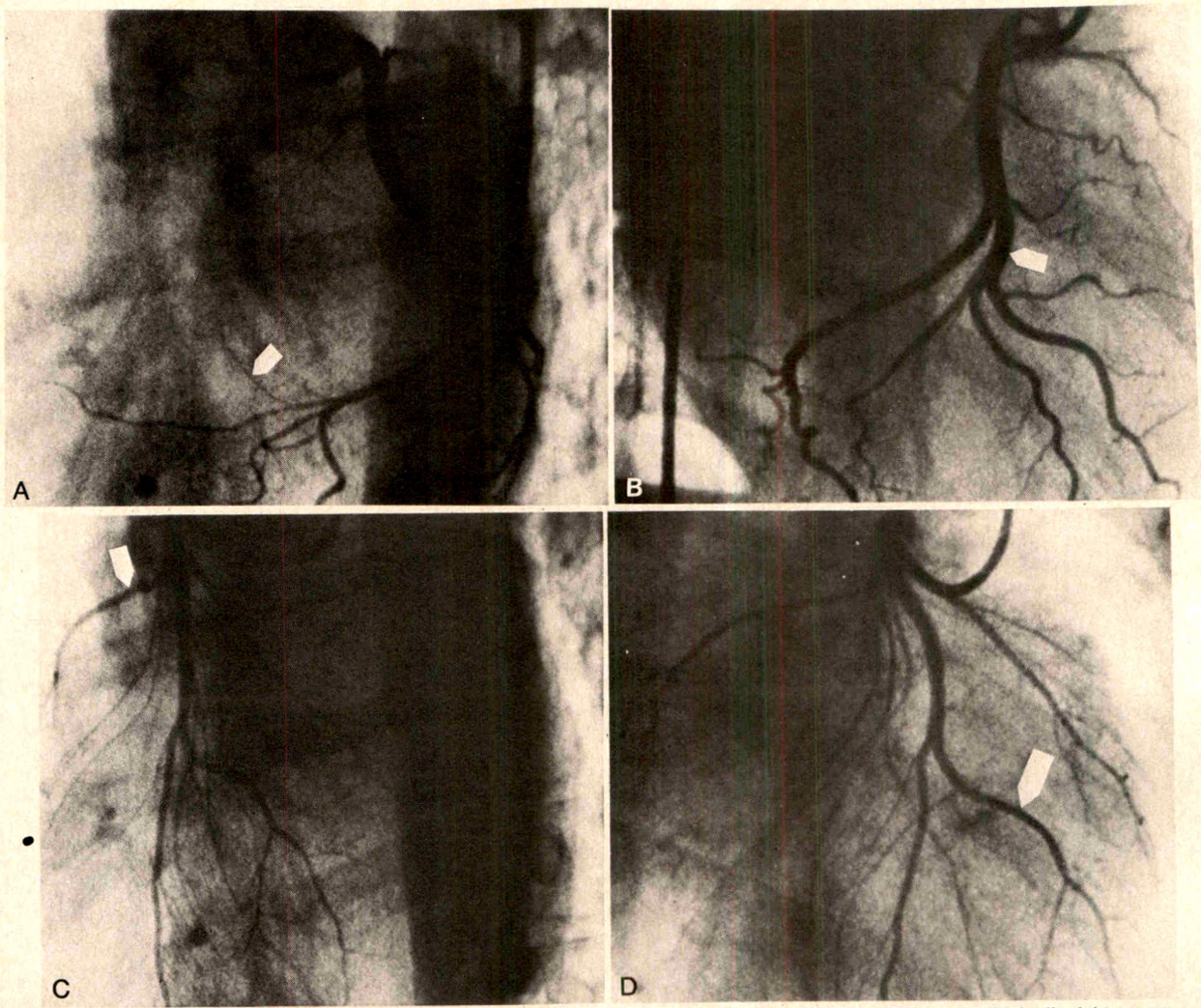

FIGURE 1. Case 1. Congenitally corrected transposition of the great arteries. **A,** selective opacification of a morphologically right coronary artery in the left anterior oblique projection. This vessel supplied blood to the morphologically right ventricle, which connected to the aorta. Note formation of the atrioventricular nodal artery (**arrow**) after the distal right coronary artery gives off its posterior descending artery. **B,** selective opacification of the morphologically right coronary in the right anterior oblique projection. Note the large size and wide distribution of the acute marginal branch (**arrow**). **C,** selective opacification of the morphologically left coronary artery in the left anterior oblique projection. This vessel supplied blood to the morphologically left ventricle, which connected to the pulmonary artery. Diagonal branches of the left anterior descending artery appear at right. Septal perforating branches are easily seen, and a small left circumflex artery is seen at left (**arrow**). **D,** selective opacification of the morphologically left coronary artery in the right anterior oblique projection. Septal perforating branches are seen at left and diagonal branches at right (**arrow**).

phologically left ventricle and the morphologically left atrium empties into the morphologically right ventricle. Thus, two separate ventricular sinuses are connected to morphologically inappropriate atria.[2] "Transposition" means that the great arteries are placed across the septum from one another and arise from morphologically inappropriate ventricles, as suggested by Van Praagh.[7] The large incidence of associated defects such as ventricular septal defect, pulmonary stenosis, A-V valve regurgitation and abnormalities in the conduction system (primarily complete heart block) abrogates the literal meaning of "corrected." Utilizing characteristic anatomic features that are identifiable on angiography, the morphologic identity of a ventricle can be established independently of its right- or left-sidedness. Similarly, the epicardial coronary arterial patterns have characteristic anatomic features that can be identified on angiography independent of whether the coronary artery originates from a right, posterior or left sinus of Valsalva.

Normal coronary anatomy: In the normal heart, the left anterior descending coronary artery represents the continuation of the main left coronary artery after the origin of the left circumflex artery. The left anterior descending artery is located in the anterior interventricular sulcus. This artery gives off septal perforating branches and terminates after curving around the apex of the heart. In the normal heart, the right coronary artery travels in the right A-V sulcus and continues to the crux of the heart where it supplies blood to the

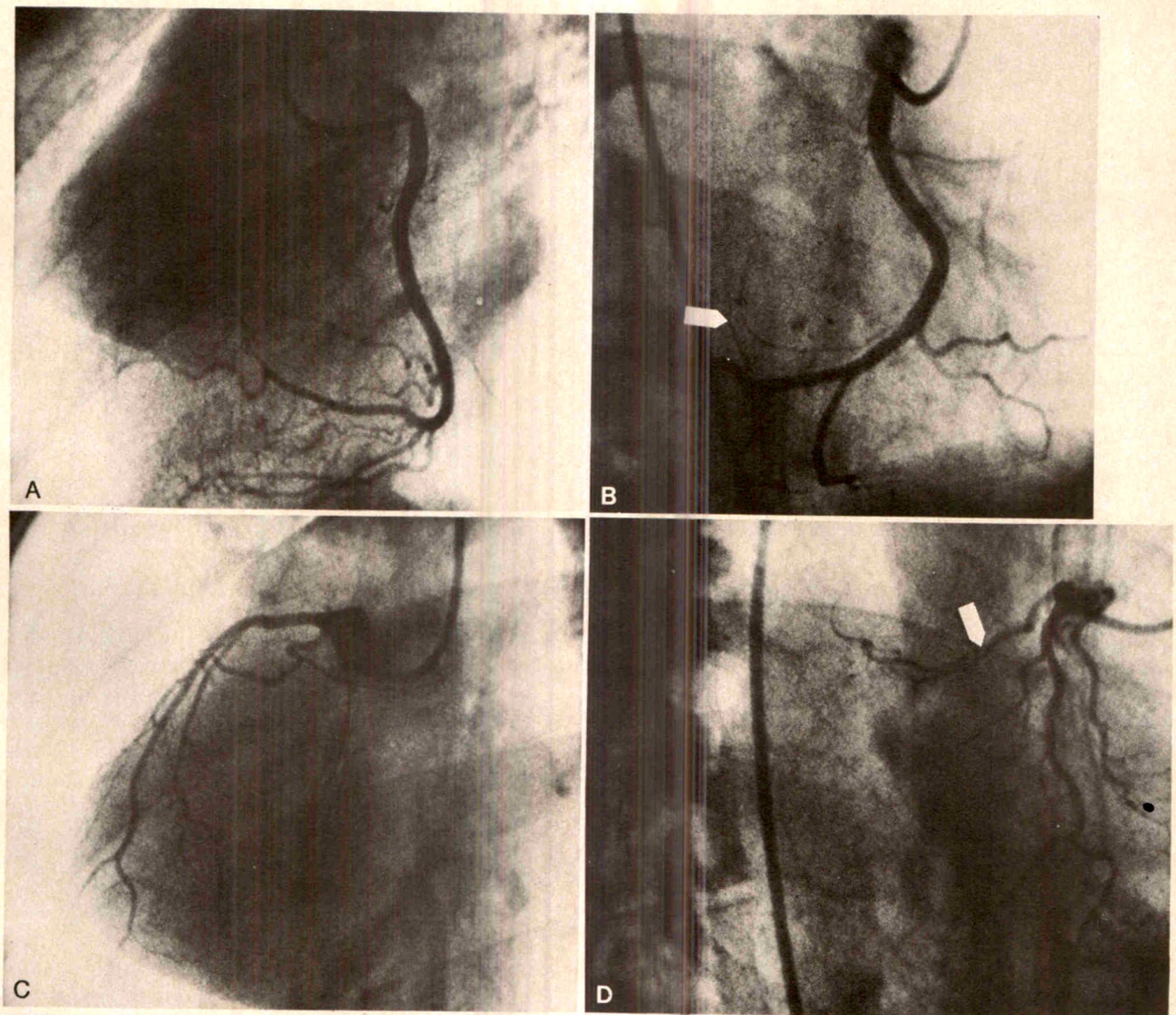

FIGURE 2. Case 2. Dextrocardia and congenitally corrected transposition of the great arteries. **A,** selective opacification of the morphologically right coronary artery in the left anterior oblique projection. This right coronary artery supplied blood to the morphologically right ventricle, which connected to the aorta. **B,** selective opacification of the morphologically right coronary artery in the right anterior oblique projection. The atrioventricular nodal artery (**arrow**) appears as the distal right coronary artery bifurcates into the posterior descending artery with its septal perforators and the posterolateral artery. **C,** selective opacification of the morphologically left coronary artery in the left anterior oblique projection. This left coronary artery supplied blood to the morphologically left ventricle, which connected to the pulmonary artery. **D,** selective opacification of the morphologically left coronary artery in the right anterior oblique projection. The left circumflex artery is small (**arrow**).

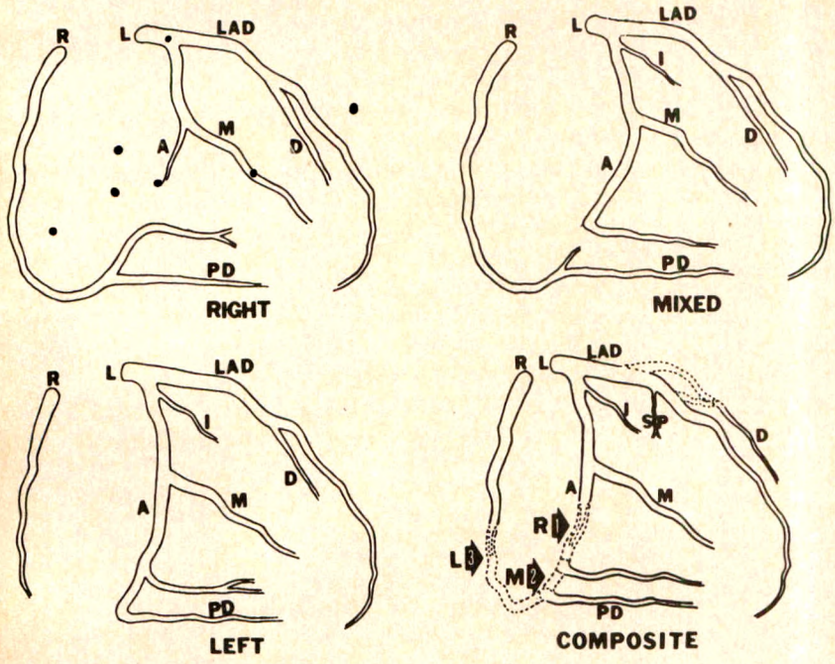

FIGURE 3. Normal coronary arterial patterns: The right system (RIGHT) in which the right coronary artery supplies the posterior descending artery and the posterolateral artery; the mixed system (MIXED) in which the right coronary artery terminates as the posterior descending artery; and the left system (LEFT) in which the atrioventricular groove vessel supplies the posterolateral artery and the posterior descending artery. The composite diagram demonstrates breaks (R-1 = RIGHT, M-2 = MIXED, L-3 = LEFT) that occur during embryogenesis and determine coronary arterial patterns. Normally, right systems are seen in 66 percent, mixed systems in 27 percent and left systems in 7 percent of cases. A = atrioventricular groove; D = diagonal; I = intermediate; L = left; LAD = left anterior descending; M = marginal; PD = posterior descending; R = right; SP = septal perforator.

posterior descending artery and part of the inferior wall of the left ventricle in 66 percent of cases.[8,9] The right coronary artery simply terminates as the posterior descending artery in 27 percent of cases and it ends at the acute margin of the right ventricle in 7 percent (Fig. 3).[8,9] In 89 percent of cases, the A-V nodal artery arises from a branch of the right coronary artery.[10] The morphologic left coronary artery can be identified anatomically as well as angiographically by the anterior descending branch with its septal perforating branches. The morphologically right coronary artery can be identified similarly by its posterior descending branch and particularly as the source of the A-V nodal artery.

Coronary anatomy in corrected transposition of great vessels: The variant anatomy of the coronary circulation in congenitally corrected transposition has been known since 1931, when Walmsley[11] described an anterior interventricular artery with septal branches as a branch of the "right coronary artery." Postmortem studies of hearts with congenitally corrected transposition have described the coronary circulation as showing an "inverted" pattern or a "mirror-image" of the normal coronary arterial pattern, implying that the anterior descending artery descends to the right of the aorta.[12–16] However, the gross appearance of the coronary pattern is normal in situs inversus.[17] Referring to such a pattern in corrected transposition as "normal" would result in loss of important developmental implications; therefore this pattern has been confusingly called a "double mirror-image" of the normal pattern.[13] The terms "morphologically left" and "morphologically right" coronary artery describe the anatomy more accurately and are consistent with the morphologic chamber identification and segmental terminology used in classifying congenital heart disease.[7]

In light of the concept of a morphologically left and right coronary arterial pattern, the present cases and those previously reported[2] suggest that the morphologically left coronary artery supplies the morphologically left ventricle and the morphologically right coronary artery supplies the morphologically right ventricle. A review of the anatomic studies of transposition complexes describing coronary anatomy supports this contention. In situs solitus, a right-sided morphologically left coronary artery and a left-sided morphologically right coronary artery were found by Schiebler et al.[13] in all 13 of their cases and by Allwork et al.[2] in all of their 29 cases. In situs inversus, a left-sided morphologically left coronary artery and a right-sided morphologically right coronary artery were found in all three cases of Allwork et al.[2]

Of the four previously reported cases illustrating the angiographic appearance of the coronary arteries in congenitally corrected transposition of the great arteries, three are consistent with this description. In the remaining case, reported by Benchimol et al.,[5] the coronary arterial pattern was not considered transposed. However, a comment was made regarding a minor abnormality of the takeoff of the vessel they described as the left anterior descending artery and the circumflex artery. We have reviewed Benchimol's published arteriograms and believe that they are consistent with a left-sided morphologically right coronary artery with a hypertrophied proximal marginal branch misinterpreted as the left anterior descending artery. In their case the right-sided coronary artery has a large septal perforator visible. This right-sided coronary artery appears to be a right-sided morphologically left coronary artery. Consequently, we can find no published anatomic or angiographic study that does not support the hypothesis that the epicardial coronary pattern

identifies the morphologic ventricle regardless of right- or left-sided spatial location of the ventricles or proximal origin of the coronary arteries from the aorta.

Embryologic implications: This consistent relation of the distal coronary anatomic pattern with the morphologic features of the ventricle supports the theory of a dual origin of the coronary arteries proposed by Ogden.[17] Angioblasts in the atrioventricular and interventricular sulci give rise to the distal epicardial coronary arteries. The proximal portion of the coronary arteries develops from the aortic coronary arterial buds. Although this bipartite origin of the coronary arteries results in numerous variations at the aortic site of development, as demonstrated by Elliott et al.[18] and Shaher and Puddu,[19] distal continuations of these arteries consistently follow a course reflecting the underlying ventricular anatomy. Therefore, the morphologically left ventricle, whether to the right (l-loop) or to the left (d-loop) of the morphologically right ventricle, is supplied by a coronary artery having the characteristics of a normal left coronary artery. In the same fashion, the blood supply to the morphologically right ventricle (l-loop or d-loop) is by way of a coronary artery that has the epicardial characteristics of a right coronary artery including the A-V nodal artery. The relative size of the vessels appears to reflect the function of the underlying ventricle. Thus in corrected transposition the morphologically right ventricle is the systemic ventricle and, consequently, the infundibular branch of the morphologically right coronary artery is large (Fig. 1B).

Angiographic implications: Several observations are in order after review of our coronary arteriograms and those previously published. Figure 3 shows the normal coronary arterial pattern familiar to the coronary arteriographer and anatomist. Right systems predominate, but both mixed and left systems are commonly seen and compatible with a normal life span. In cases of congenitally corrected transposition of the great arteries in which selective coronary arteriograms are available, only right systems are seen (Fig. 4), perhaps because of a sampling error or possibly a natural selective process operating against small morphologically right coronary arteries. The right coronary artery in right systems appears best able to develop to meet the coronary arterial demands of the systemic ventricle. In any event, should a left system be found in the setting of corrected transposition, then the A-V nodal artery may not be an anatomic marker for the morphologically right coronary artery.

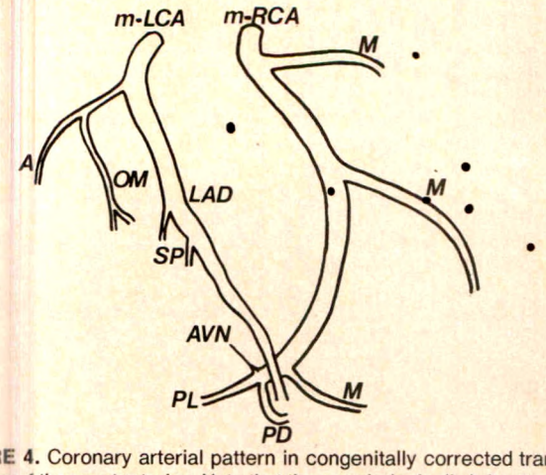

FIGURE 4. Coronary arterial pattern in congenitally corrected transposition of the great arteries. Note that the morphologically left anterior descending (LAD) branch crosses the morphologically right coronary artery (RCA) in this slight right anterior oblique projection in contrast to the normal diverging pattern seen in Figure 3. A = atrioventricular groove; AVN = atrioventricular node; M = marginal; m-LCA = morphologically left coronary artery; m-RCA = morphologically right coronary artery; OM = obtuse marginal; PD = posterior descending coronary artery; PL = posterolateral coronary artery; SP = septal perforator.

Morphologic identification from a visual pattern alone can be deceiving. For example, the similar appearance of Figures 1A and 2A is misleading, particularly when one considers that they were obtained from patients with levocardia and dextrocardia, respectively. Also, the lack of similarity of Figures 1C and 2C may be confusing. These similarities and differences can be explained by expected rotational changes due to levo- or dextrocardia, by relative rotations because of enlargement of a specific cardiac chamber and, most particularly, by the underlying ventricular looping. The use of angiographically identifiable anatomic features allows for accurate morphologic identification of the coronary artery regardless of rotational changes resulting from levo- or dextrocardia or from associated cardiac defects. Thus, in complex congenital heart disease in which the intraventricular morphologic features are not well defined, the angiographic characteristics of the epicardial coronary arterial pattern may permit accurate identification of the ventricles.

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Two Dimensional Echocardiography in Differentiating Right Atrial and Tricuspid Valve Mass Lesions

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Atrial myxoma has been diagnosed on the basis of a characteristic M mode echocardiographic pattern of a mass of echoes appearing, with a lag phase, beneath the anterior leaflet of the mitral or tricuspid valve in diastole. However, this pattern is not specific for an atrial tumor. Two patients are described with tricuspid leaflet endocarditic vegetations whose M mode echocardiograms were strikingly similar to the M mode tracing from a patient with a large right atrial myxoma. In a fourth patient, artifact, resulting from the failure of lateral resolution of the atrial wall, was also capable of producing a mass of echoes appearing, with a lag phase, beneath the anterior tricuspid valve leaflet in diastole. In each patient, two dimensional echocardiography confirmed the presence or absence of a right-sided mass lesion and defined more precisely the location of the echocardiographic density relative to the right atrium and tricuspid valve. Because two dimensional echocardiography is capable of detecting anatomic relations in two distance dimensions and of visualizing movement of intracardiac structures relative to one another in real time, it can play an important role in the identification and differential diagnosis of intracardiac mass lesions.

The echocardiogram has achieved a major role in the diagnosis of intracardiac myxomas[1–14] and in the detection of valve vegetations.[15–27] Although the echocardiographic appearance of myxomas and valve vegetations is usually quite different, we have seen one patient with a right atrial myxoma and two patients with tricuspid valve endocarditis whose M mode echocardiograms were strikingly similar, showing a mass of echoes appearing beneath the anterior leaflet of the tricuspid valve in diastole. In each case there was a lag phase between opening of the anterior leaflet and the appearance of the echocardiographic density, a finding characteristic of a myxoma. In addition, with certain transducer angulations, the atrial wall may be visualized below the anterior leaflet of the tricuspid valve, creating a similar pattern of a mass of echoes appearing, with a lag phase, beneath the anterior leaflet of the tricuspid valve in diastole. This technical artifact has been produced by us in several cases and is illustrated by the fourth case. In each case presented, the two dimensional echocardiogram was helpful in confirming the presence or absence of a right-sided mass lesion and in defining more precisely the location of the echocardiographic density relative to the right atrium and tricuspid valve.

Methods

The M mode and two dimensional echocardiographic studies in each patient were performed with the patient's chest elevated 15° and with the patient turned very slightly into a left lateral position.

M mode echocardiograms: These echocardiograms were obtained using an Irex System II Ultrasonoscope, coupled with a 2.25 megahertz transducer focused at 7.5 cm, and were recorded on an Irex System II recorder. The echocardio-

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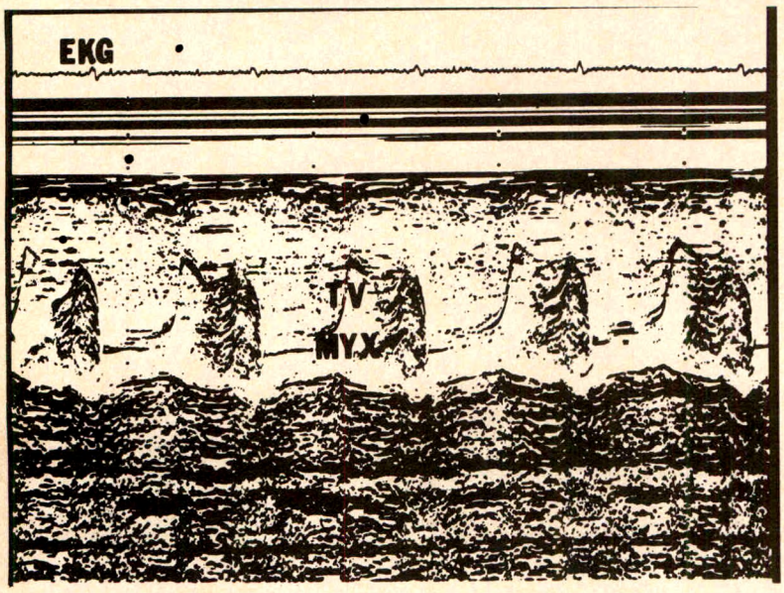

FIGURE 1. Case 1. M mode echocardiographic recording of the tricuspid valve (TV). The mass of echoes produced by the right atrial myxoma (MYX) appears, with a lag phase, between the tricuspid valve leaflets during mid diastole. EKG = electrocardiogram.

graphic transducer was placed along the left sternal border in the third to fourth intercostal space and angled to record echoes from the mitral valve. The transducer was then angled inferiorly and laterally to record echoes from the left ventricular cavity and superiorly and medially to record echoes from the aortic root and left atrium. The transducer was angled medially from the region of the mitral valve in order to record echoes from the triscuspid valve.

Two dimensional echocardiographic scans: These scans were obtained in multiple planes using the 80° Varian, model 3,000, phased array sector scanner. A long axis view of the heart, approximating a sagittal plane, was obtained by positioning the transducer in the third to fourth intercostal space to the left of the sternum and directing the plane of the sweep from the inferior wall of the left ventricle to the base of the heart. Four chambered views from the apex were obtained by positioning the transducer at the apex and angulating it to visualize both right and left atria and right and left ventricles in the same plane; this method has been described by Silverman and Schiller.[28] The two dimensional images were displayed on an oscilloscope at a rate of 30 frames/sec. They were recorded and stored on video tape at a rate of 30 frames/sec. Polaroid® or 35 mm photographs were made from the video tapes.

Case Reports

Case 1: A 57 year old woman with a history of exertional chest tightness and dyspnea was admitted to the hospital when an electrocardiogram showed slight S-T segment elevation and T wave inversion in leads V_1 to V_4. Physical examination revealed a prominent *a* wave in the jugular venous pulse and an early diastolic sound at the left sternal border

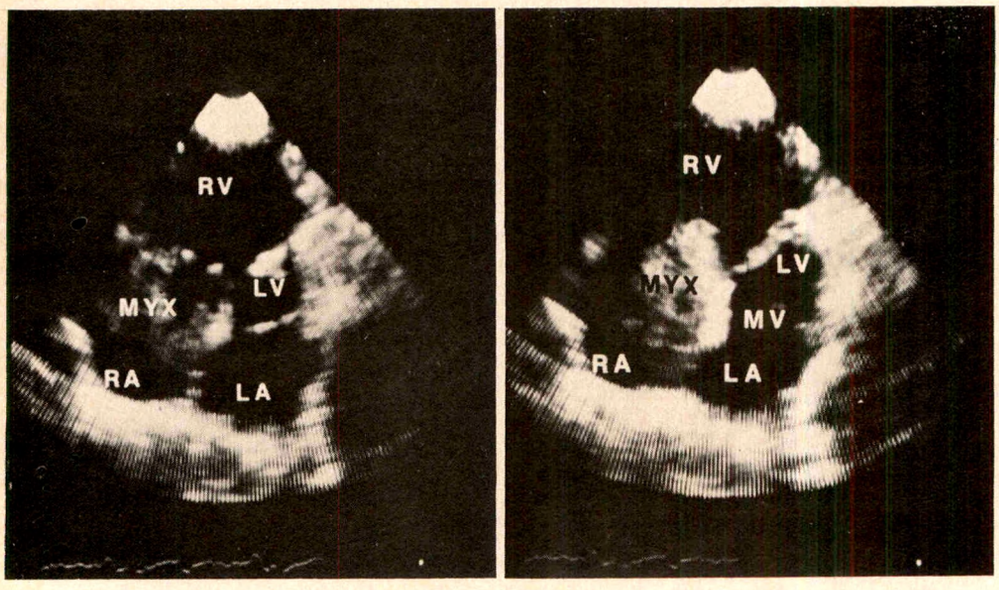

FIGURE 2. Case 1. Two dimensional apical view of the four cardiac chambers. **Left,** in the systolic frame, the mass of echoes produced by the myxoma (MYX) is contained within the right atrium (RA). **Right,** during diastole, the myxoma is seen to descend into the right ventricle (RV). LA = left atrium; LV = left ventricle; MV = mitral valve.

during inspiration, confirmed on phonocardiographic recording to occur 0.16 second after the aortic component of the second heart sound. The electrocardiogram subsequently evolved additional T wave inversions in the inferior leads, but the cardiac enzyme serum levels remained normal.

An echocardiogram, obtained to assess the possibility of pericarditis, showed no effusion but disclosed slight right ventricular enlargement (2.7 cm in diameter) and a mass of echoes appearing, with a lag phase, beneath the anterior leaflet of the tricuspid valve in diastole (Fig. 1). The E-F slope of the tricuspid valve was normal at 85 mm/sec. With use of the four chambered view from the apex, two dimensional echocardiography (Fig. 2) demonstrated a large right atrial mass attached to the interatrial septum by a broad stalk. The mass of echoes was separated from the tricuspid valve and confined to the right atrium during systole and prolapsed between the tricuspid valve leaflets into the right ventricle during diastole. There was no evident left atrial mass on M mode or two dimensional echocardiographic examination.

Cardiac catheterization revealed normal coronary arteries and confirmed the presence of a right atrial mass prolapsing through the tricuspid valve in diastole. A right atrial myxoma, 6 by 5 by 3 cm, weighing 31 g was removed at operation.

Case 2: A 25 year old female heroin addict without a past history of cardiovascular disease was admitted to this hospital with a fever of 104° F. Physical examination revealed an ejection murmur and an intermittent systolic click at the left lower sternal border. Blood cultures were positive for alpha streptococci.

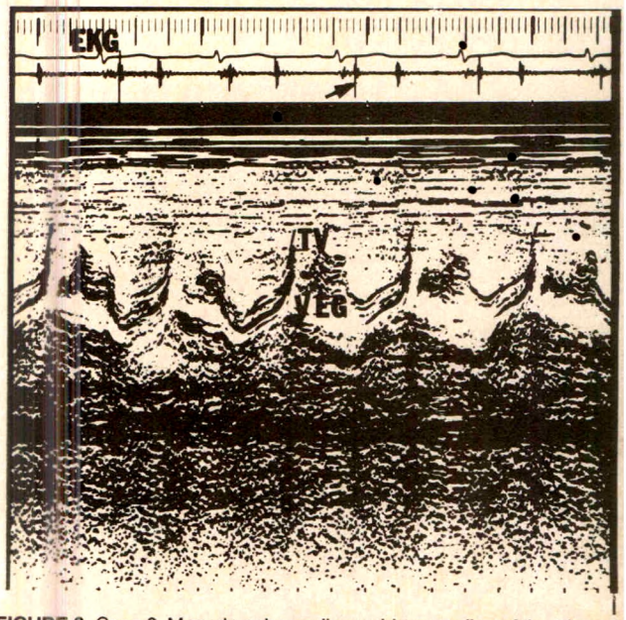

FIGURE 3. Case 2. M mode echocardiographic recording of the tricuspid valve (TV) showing a mass of echoes representing vegetations (VEG) appearing beneath the anterior leaflet of the tricuspid valve in diastole. A lag phase is seen between opening of the tricuspid valve and the appearance of the abnormal echoes. A prominent early systolic sound **(black arrow)** was recorded on the phonocardiogram at the lower left sternal border. EKG = electrocardiogram.

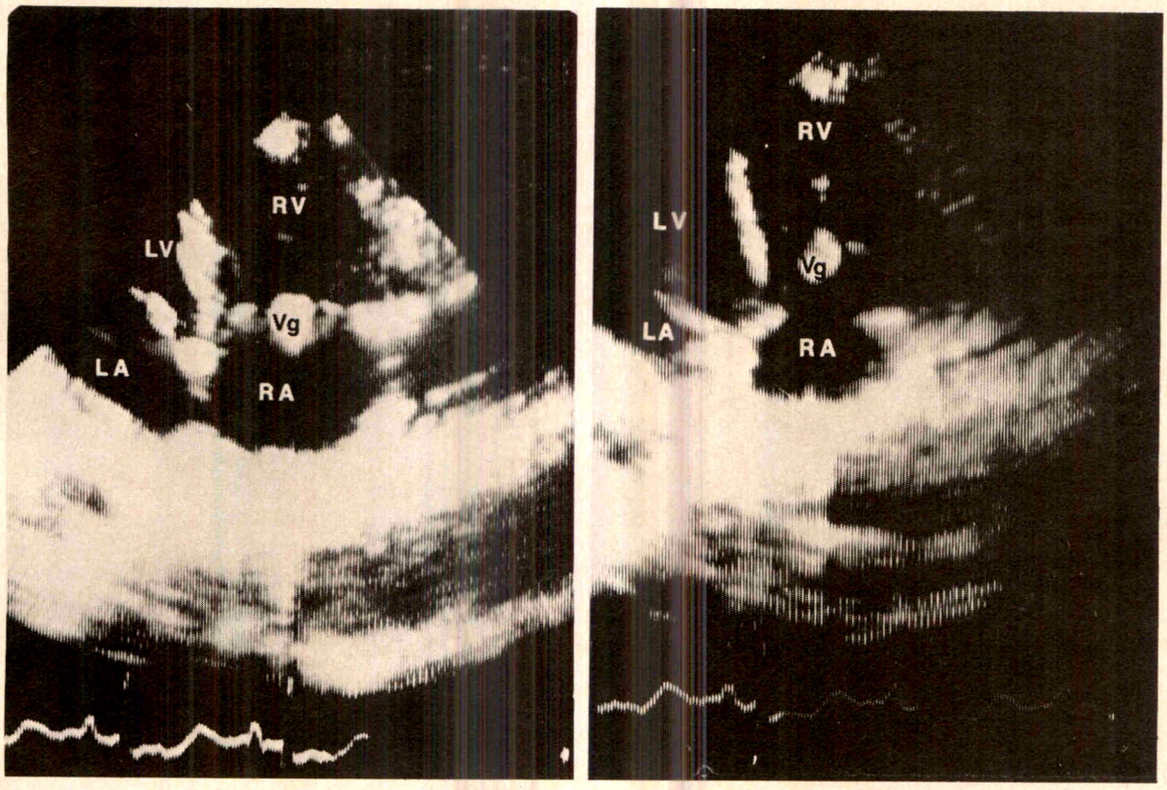

FIGURE 4. Case 2. Two dimensional apical views of the four cardiac chambers during systole **(left)** and diastole **(right). Left,** a mass of echoes, interpreted to represent vegetations (Vg) of the tricuspid valve, is seen on the tricuspid valve closure line during systole. **Right,** the echo mass moves into the right ventricular (RV) cavity with the tricuspid valve septal leaflet during diastole. An electrocardiogram is recorded below the echocardiogram. LA = left atrium; LV = left ventricle; RA = right atrium.

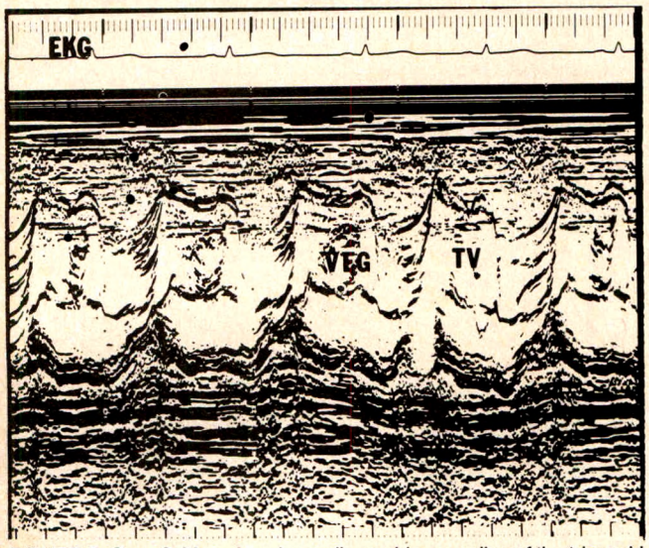

FIGURE 5. Case 3. M mode echocardiographic recording of the tricuspid valve (TV) showing a mass of echoes, thought to represent vegetations (VEG), between the two visualized leaflets of the tricuspid valve. EKG = electrocardiogram.

On M mode echocardiographic examination the aortic and mitral valves appeared normal, but there was an abnormal mass of echoes, appearing with a lag phase, beneath the anterior leaflet of the tricuspid valve during diastole (Fig. 3). The tricuspid valve was well visualized with two dimensional echocardiography with use of the four chambered apical view (Fig. 4). A large circular mass of echoes was seen to be adherent to the distal end of the septal tricuspid leaflet and moved with the tricuspid valve, descending into the right ventricular cavity during diastole. No mass was seen within the right atrial cavity.

A diagnosis of tricuspid valve endocarditis was made and the patient received 5 weeks of therapy with antibiotic drugs. One week after completion of therapy she was reevaluated for recurrent fever and the new onset of left-sided pleuritic pain. There were no signs of leg vein thrombosis. Chest X-ray film was normal, but the lung scan revealed a left basilar perfusion defect compatible with a pulmonary embolus. Repeated blood cultures were negative. The M mode echocardiographic study was similar to the previous study but, on two dimensional examination, the nodular mass adherent to the septal leaflet of the tricuspid valve was seen to be considerably smaller than on the examination 6 weeks previously. The diagnosis of a pulmonary embolus, presumably arising from a sterilized tricuspid valve vegetation, was made. The patient recovered uneventfully and was discharged.

Case 3: A 26 year old heroin addict with a murmur known since childhood was admitted with arthralgias, rigors, weight loss and a fever of 104° F. Physical examination revealed a left conjunctival hemorrhage and a holosystolic murmur that increased with inspiration and was heard along the left sternal border. Blood cultures were positive for Staphylococcus aureus.

M mode echocardiographic examination revealed pansystolic sagging of the mitral valve leaflets, compatible with mitral valve prolapse and, from some angles, sagging of the tricuspid valve leaflets suggesting tricuspid valve prolapse. There were no apparent aortic or mitral leaflet vegetations, but a mass of echoes was seen between the anterior and posterior tricuspid valve leaflets in mid diastole (Fig. 5). On two dimensional examination, the two tricuspid valve leaflets that were visualized appeared to have slight focal thickening. No large valve mass was visible and there was no apparent atrial tumor. The patient recovered uneventfully with antibiotic treatment. The M mode echocardiogram after treatment with antibiotic drugs revealed no change.

Case 4: An asymptomatic 20 year old man with Marfan's syndrome was found on an M mode echocardiographic examination to have pansystolic sagging of the mitral and tricuspid valve leaflets, compatible with prolapse, and dilatation of the proximal aortic root. From some angles of the examination, a mass of echoes was visualized behind the anterior leaflet of the tricuspid valve, appearing in early diastole, but lagging slightly behind the opening of the tricuspid valve (Fig. 6). With scanning from the tricuspid valve to the region of the aortic root and left atrium, the mass of echoes was seen to separate from the region of the tricuspid valve and to be continuous with the atrial wall, suggesting that the mass of echoes represented diastolic movement of the atrial wall. No mass was apparent in the right atrium or in the region of the tricuspid valve leaflets on two dimensional echocardiographic scanning. Similar artifactual echoes behind the anterior leaflet of the tricuspid valve in diastole have since been produced in other patients when an attempt was made to visualize the tricuspid valve from multiple angles.

Discussion

The M mode echocardiographic appearance of an atrial myxoma has been so characteristic that some cardiologists and surgeons have suggested that angiographic confirmation may not be necessary before operative intervention.[2,29] The tumor, which is more commonly located in the left than in the right atrium,[30] can be recognized by a mass of echoes that descend below the anterior leaflet of the mitral or tricuspid valve during diastole.[3,5,6,9,12] A lag phase is characteristically noted between initial opening of the mitral or tricuspid valve and the time of appearance of this abnormal mass of echoes.[2,3,5,6,12] The E-F slope of the valve is frequently decreased, presumably as a result of obstruction of atrial emptying caused by the myxoma. A left atrial myxoma can usually be identified within the left atrial cavity during systole.[6,13] Although new angulation techniques may prove useful in visualizing the interatrial septum,[12] the right atrium is a difficult structure to identify with M mode echocardiographic techniques and the presence of a right atrial myxoma is frequently suspected only from the abnormal diastolic echoes below the tricuspid valve. Endocarditic vegetations can be recognized as shaggy or irregular echoes that are adherent to a valve leaflet. They typically do not interfere with leaflet movement.[15–27]

Right atrial myxoma versus tricuspid valve vegetation: In our four cases, M mode echocardiograms were all similar in showing a mass of echoes appearing beneath the anterior leaflet of the tricuspid valve and visible only in diastole. In each case, the appearance of the abnormal echoes lagged considerably behind the opening of the tricuspid valve leaflets. When best seen, the tricuspid valve E-F slope in each case was normal. Differentiation of leaflet vegetations from an atrial mass prolapsing through the tricuspid valve was thus not possible with M mode scanning alone. The positive

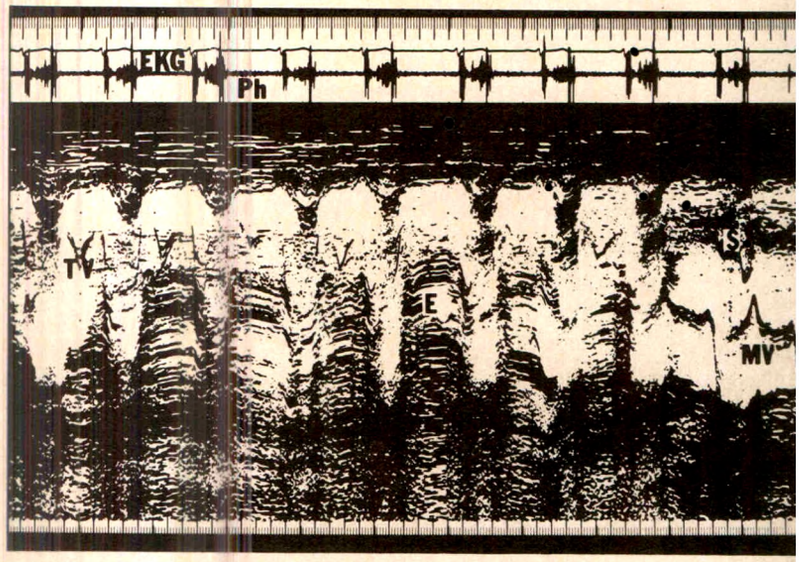

FIGURE 6. Case 4. M mode echocardiographic recording of the tricuspid valve (TV) demonstrating a mass of echoes (E) appearing, with a lag phase, beneath the anterior leaflet of the tricuspid valve in diastole. A scan toward the mitral valve (MV) suggests that the abnormal echoes may have been produced by the atrial wall. EKG = electrocardiogram; Ph = phonocardiogram at the apex, demonstrating a late systolic murmur; S = septum.

blood cultures in Patients 2 and 3 were supportive of leaflet vegetations, but myxoma could not be excluded because infection of the latter has been reported.[31] However, with two dimensional echocardiography, which allows visualization of anatomic relations and movement of intracardiac structures relative to one another in two distance dimensions, it was possible to differentiate a myxoma arising in the right atrium from a focal tricuspid valve mass in Patients 1 to 3 and to confirm as artifactual the abnormal echoes in Patient 4. In patient 1, the large mass was seen to fill the right atrium during systole. It was connected to the interatrial septum by a broad stalk and appeared entirely separate from the tricuspid valve leaflets in systole. After opening of the tricuspid valve there was a lag phase followed by prolapse of the mass into and partially through the tricuspid valve leaflets. In Patient 2, a large mass was seen on the septal leaflet of the tricuspid valve. It moved in concert with the tricuspid leaflet throughout the phases of the cardiac cycle. One month later, after a pulmonary embolus developed, the tricuspid valve mass was found to be greatly diminished in size, suggesting that the embolus might have arisen from a healed tricuspid leaflet vegetation. In Patient 3, there was slight focal thickening of the septal tricuspid leaflet. The tricuspid valve appeared normal in Patient 4. In both Patients 2 and 3, no right atrial mass was visualized on two dimensional echocardiographic study, further supporting differentiation between a right atrial myxoma and an endocarditic vegetation. In Patient 4 and in subsequent patients with similar M mode echocardiographic findings, two dimensional scanning revealed neither a right atrial mass nor an abnormality of the tricuspid valve, thus supporting a diagnosis of echocardiographic artifact.

Two dimensional versus M mode echocardiography: Because of its abilities to detect anatomic relations in two distance dimensions, to visualize movement of structures relative to one another in real time and to scan the heart in multiple planes, two dimensional echocardiography will probably assume a major role in the identification and differential diagnosis of intracardiac mass lesions. Two dimensional echocardiography can assist in the identification of echocardiographic artifacts that may mimic the M mode echocardiographic patterns of actual disease and will be of special importance in those patients whose endocarditic vegetations located on the tricuspid valve,[15] as in our patients with endocarditis, or on the mitral valve,[25] produce an M mode echocardiographic pattern similar to that of a right or left atrial mass. Differentiation of an endocarditic vegetation from the rare myxoma that arises from valve tissue[32] may be difficult in the case of a small tumor but may be possible with two dimensional echocardiography when the myxoma is large and pedunculated.

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How Should Refractory Ventricular Tachycardia Be Treated?*

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I can see it now. In a soon to be released major motion picture, Q will present to James Bond a gunlike device that, when pointed at a victim, will silently produce ventricular tachycardia. Death will be ascribed to a heart attack, and no evidence of Agent 007's well known license to kill will be found. Actually a gun to induce ventricular tachycardia has been developed. It is called an electrode catheter, and the energy source is a programmed stimulator.

Whereas Bond would not need an "effective therapeutic modality" (what an ungracious phrase) for his induced ventricular tachycardia, physicians are frequently called on to treat this most alarming condition. Ventricular tachycardia produces uncomfortable, disabling symptoms, frequently develops in patients with other severe cardiac disabilities, is recurrent, not isolated, and can be fatal. The frequent visits to emergency wards for conversion to sinus rhythm and the repeated admissions to the intensive care unit of the hospital frighten the patient and his family and frustrate the physician who is seeking remission of the problem. When a cardiologist thinks about the most troublesome condition that he is called upon to treat, surely ventricular tachycardia would be at or near the top of his list.

Three programs are available for the treatment of ventricular tachycardia: drugs, pacing and surgery. The purpose of each is basically the same, to disengage the operation of a reentrant circuit within the heart either by pharmacologic suppression, electric stimulation or operative removal. Treatment with drugs and in some centers with pacing is always tried first. When medicine fails, and the patient's ventricular tachycardia is deemed "refractory," operation is considered.

Aneurysmectomy: Does It Work?

Cardiac surgery for treatment of refractory ventricular arrhythmias has been applied most successfully in patients with ventricular aneurysm. The operation is not new. Ventricular aneurysmectomy primarily for arrhythmia control has been performed for more than 20 years.[1,2] It is presumed that the operation works for one or more of three reasons: (1) The origin of the ventricular tachycardia has been removed and sent to the pathologist in the leather-like fibrotic tissue that was once contracting myocardium; (2) improvement in ventricular function has been produced with removal of the aneurysmal receptacle into which a portion of the left ventricular output was wastefully projected during systole; or (3) the heart has been rendered less ischemic because it functions better and may now be supplied with more blood thanks to coronary arterial bypass grafting performed in association with the aneurysmectomy.

In considering the safety and effectiveness of aneurysmectomy with or without coronary bypass grafting in relieving patients of ventricular tachycardia, one must answer several questions: What is the operative mortality? What is the long-term mortality? How many patients no longer have ventricular tachycardia with or without antiarrhythmic drug therapy?

Operative mortality can be easily reviewed by examining the reported studies. However, long-term survival is somewhat more difficult to assess because of the variation in the intensity of the follow-up survey and in the length of time since operation.

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Even more serious problems arise in trying to decide just how many patients have truly been relieved of the arrhythmia. To answer the question fully, follow-up evaluation must be compulsively conducted with frequent recordings of tape-recorded electrocardiograms during everyday activity. Less comprehensive but clinically important data can be obtained by recording the patient's awareness of the symptoms of ventricular tachycardia with documentation in standard electrocardiograms. If we assume that the past can teach us, it seems likely that the more we look for ventricular tachycardia in a susceptible patient both before and after operation, the more we will find it.

Recent reports: Two articles that directly address these problems have recently been published in this Journal.[3,4] Each supplies useful information, but each points out the problems the reader meets in evaluating the effectiveness of treatment from different institutions. Some of the important data are summarized in Table I along with the most recent results of our own experience at the Hospital of the University of Pennsylvania.

In this issue of the Journal, Buda et al.[4] report from Stanford University on a large group of patients treated for refractory ventricular tachycardia with aneurysmectomy augmented in some cases by coronary bypass grafting. The operative mortality seems quite acceptable when one considers the severe illness that afflicted most of the patients. Particularly striking was the fate of 7 of the 56 patients (13 percent) who died perioperatively from ventricular arrhythmias. It must be concluded in each of these cases that the procedure did not eliminate the primary problem.

Most of the patients, however, seem to have been helped. Although antiarrhythmic drugs are still needed for 20 of the 35 long-term survivors (57 percent), 24 (69 percent) are asymptomatic and 11 (31 percent) have nondisabling symptoms. Recurrent ventricular tachycardia has been observed in four survivors; if these patients are added to the seven who died, it is evident that ventricular tachycardia was not successfully treated in at least 11 of 56 (20 percent). The nature of the follow-up—without Holter monitoring in *all* survivors or electrophysiologic study in any—raises the question whether ventricular tachycardia may be present, albeit without limiting effects, in some of the other patients.

The earlier report by Wald et al.[3] in this Journal raises other interesting aspects of the problem. Ventricular aneurysmectomy with or without coronary bypass grafting was performed in 13 patients at the Toronto General Hospital. Five patients died in the perioperative period. Of these five, four underwent operation within 4 weeks of myocardial infarction. The high operative mortality rate soon after acute infarction has been mentioned in other reports including that of Buda et al.[4] Nevertheless, the surgical treatment clearly produced greater survival than in a similarly ill group of patients treated without operation by the Toronto group.

The methods used by these and most of the other groups who have reported their experiences are quite similar. Only recently have the lessons learned from the experimental electrophysiologic laboratory and from the operative treatment of preexcitation been applied to patients with ventricular tachycardia. The contemporary approach is based on the assumption that most ventricular tachycardia is due to the phenomenon of reentry.

Reentry—The Common Mechanism of Ventricular Tachycardia

That reentry is the mechanism in the great majority of cases of ventricular tachycardia has been established to the satisfaction of most, though not all, investigative electrocardiographers and clinical electrophysiologists. It taxes the imagination to devise a better concept to explain the many studies on ventricular tachycardia that show how programmed stimulation can repeatedly initiate and terminate episodes of the arrhythmia with reproducible techniques. No one has yet conclusively demonstrated in human beings how any mechanism other than reentry can account for these results as obtained in the clinical electrophysiology laboratory.

Clinical electrophysiologic testing—the basis of the new approach: Our ability to initiate and terminate ventricular tachycardia by programmed stimulation forms the basis for the contemporary management of refractory cases.[5,6] Without such study, therapeutic success must be guided only by the patient's report of symptomatic relief and the absence of the arrhythmia on standard or extended electrocardiographic monitoring. Use of these criteria for therapeutic success is adequate in some cases, but when repetitive episodes of ventricular tachycardia occur despite administration of apparently adequate drug treatment, then a more satisfactory effort to suppress the arrhythmia is needed.

Most cardiologists probably do not realize that a close correlation has been demonstrated between the data obtained from drug testing in the electrophysiology laboratory and the later *clinical* response of the patient.[7,8] When a drug has made it impossible to initiate sustained ventricular tachycardia, the likelihood is high that the drug evaluated in the laboratory will be effective at a similar blood level when the patient goes home.

In our experience, effective programs can be developed with conventional antiarrhythmic drugs for about half of those patients referred with "refractory" ventricular tachycardia. Lidocaine or tocainide (or both), procainamide, quinidine, disopyramide and phenytoin are first evaluated with highest tolerated doses. Only after all standard drugs have been found to be ineffective in preventing induced sustained ventricular tachycardia, do we turn to permanently installed intermittent pacing, experimental drugs or operation. We only break this rule when disabling angina or congestive heart failure is prominent. Then surgical procedures including aneurysmectomy, valve placement or coronary bypass grafting may be indicated even though the arrhythmia could have been controlled with drugs alone.

Evaluation for Operation

At this point the patient must be fully evaluated as a possible candidate for operation. Left ventriculography is performed and the films are carefully searched for demonstration of a ventricular aneurysm or an area of relatively discrete infarcted tissue. We and many other workers shy away from operating on the small number of patients with refractory ventricular tachycardia who have diffuse noncoronary disease such as cardiomyopathy. Coronary arteriography is also performed so that coronary bypass grafting will be added when indicated. Few patients who have not recently sustained an acute myocardial infarction need to be rejected for this operation even if their ejection fraction is depressingly low.

Epicardial and Endocardial Mapping

Unlike the practice at most institutions, including those whose reports have just been discussed, at our hospital epicardial and endocardial mapping is used to guide the surgeon in his quest for the focus of the ventricular tachycardia (Drs. Leonard N. Horowitz and Mark E. Josephson do the guiding and Dr. Alden H. Harken does the questing and resecting).

Experimental basis: The technique has its origin in animal experiments that, for the most part, have subsequently been supported by work in the operating room. That the origin of ventricular tachycardia could be reproducibly identified was demonstrated by epicardial mapping in dogs intoxicated with digitalis.[9] It was then shown that in ventricular tachycardia induced by ischemia and infarction the arrhythmias began, as long suspected, in the subendocardial Purkinje tissues and that the electric activity might "break through" on the epicardial surface at a location that was not directly above the endocardial site of origin.[10,11] The data from the animal laboratory suggested that in human ventricular tachycardia *endocardial* mapping would probably be necessary for accurate localization of the focus.

The goal of this work was to devise a therapeutic technique analogous to that used by neurosurgeons for more than 30 years in the treatment of epilepsy.[12] "Find the source and cut it out" might be considered the battle cry of those working in the field.

Data from the operating room: In the operating room itself, several interesting observations have come to light just from the mapping studies themselves. First, it has been shown that the location of the focus cannot be predicted with certainty from the morphologic features of the ventricular tachycardia in the electrocardiogram.[13] Many examples of ventricular tachycardia with the form of left bundle branch block originate in the left rather than in the right ventricle as would have been expected. These results, confirmed recently by intraoperative mapping, had been suggested by data obtained from endocardial mapping conducted in the cardiac catheterization laboratory.[14,15] It also appears that ventricular tachycardias with different electrocardiographic forms in the same patient may originate from the same site, the changing pattern being a function of various sites of exit or conduction from the reentrant focus.[15]

TABLE I

Operative Mortality and Relief of Ventricular Tachycardia (VT) in Three Series of Patients Who Underwent Ventricular Aneurysmectomy With or Without Coronary Arterial Bypass Graft Surgery

Report	Operative Mortality	Patients Relieved of VT
Wald et al.,[3] 1979	5 of 13 (39%)	Contribution of VT to death not noted; no survivors have intractable VT
Buda et al.,[4] 1979	11 of 56 (20%)	45 of 56 (80%)
Hospital of the University of Pennsylvania, 1979	2 of 29 (7%)	26 of 29 (90%)

Of greater practical importance has been the confirmation of the finding in animals that the epicardial breakthrough may be distant from the site of origin in the subendocardium.[13] Thus, epicardial mapping alone may mislead the surgeon into removing tissue remote from the site of origin. Finally, it appears that the ventricular tachycardia does not usually begin within the aneurysm itself despite the obvious local pathologic features and abnormal electrophysiologic findings.[16]

Endocardial resection: After the surgeon has performed a conventional aneurysmal resection, the patient's ventricular tachycardia can in almost all cases still be restarted with programmed stimulation. The maps then reveal that the earliest point of depolarization during ventricular tachycardia is in subendocardial tissue adjacent to the line of aneurysmal excision and grossly normal in appearance. Removal of this portion of the inner lining of the contracting myocardium makes it impossible to restart the ventricular tachycardia.

Is Mapping Necessary?

Cardiologists, cardiac surgeons and others especially interested in the treatment of ventricular tachycardia have questioned whether mapping is necessary. Can't an operation be fashioned whereby the site of the arrhythmia can be resected without the collaboration of an electrophysiologic team with its associated personnel and time? We do not yet know the answer to this question. Strictly comparable data from patients who have had operation—some with and some without mapping—are unavailable. Even the techniques employed for mapping and operation are different, and the series reporting the use of one specific technique have until now been relatively small.[17–24]

Local experience: At our institution we have observed a 90 percent remission rate in a group of 29 patients in whom mapping and operation were performed with a similar technique (Table I). Two of the 29 died perioperatively, both with cardiogenic shock and both with evidence of very recent myocardial infarction at autopsy. Neither of these patients had ventricular

tachycardia on the day after operation when they were being observed with constant monitoring. Three other patients still have ventricular tachycardia, although the arrhythmia can now be controlled with drugs, which was not possible before the operation. In each case, for technical reasons, the surgeon could not remove the locus determined with mapping in the catheterization laboratory and the operating room. None of the remaining 24 patients has required antiarrhythmic drugs for suppression of ventricular arrhythmias (one takes quinidine for paroxysmal atrial fibrillation).

Each surviving patient has been fully studied postoperatively in the electrophysiology and angiography laboratories. Sustained ventricular tachycardia could be induced only in the three patients whose clinical ventricular tachycardia persists. The left ventricular angiograms suggest that the endocardial excision has in no obvious manner directly and specifically impaired left ventricular function.

Evaluating the results: My own admittedly biased opinion is that mapping, as carried out in our hospital, works and that the results of the operation will be better when the origin of the ventricular tachycardia is located and specifically removed. The amount of time added by the mapping itself once the team has been fully trained is almost trivial—only about 15 minutes in our most recent cases. I also maintain that in order to know whether *any* procedure is effective, electrophysiologic studies should be conducted before and after the procedure. Then Holter monitoring should be performed in *all* survivors at periodic intervals. Only by searching prospectively as thoroughly as possible for residual arrhythmias can the success of the different methods of treatment be fully evaluated.

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Vexatious Expressions in Current Medical Writing*

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This essay deals with the quality of medical writing. Communication is difficult. It is said that the construction of an error-free declarative sentence is a challenge. Most of us can write better than we do. I share the general prejudice that medical writers, like most writers, not only wish their papers to be published but also wish them to be read. Few of us would write if our communications were to be printed and then dropped into the sea, never to be seen again. I submit that better writing not only communicates ideas clearly, but also is more likely to be read, reread and remembered.

During 15 years and more of reading, writing and editing, I have met with a number of common expressions that detract from medical writing. I find these expressions vexatious because they fall harshly on my ear, which first became familiar with general English; medical English came later. Some of these expressions we share in common with modern American English; others are peculiar to medical writing. In the following effort, I admit the prejudice that good medical writing should be as much like good general English writing as possible. Medicine, like other technical fields, must have its own vocabulary, but only for matters for which there is no equivalent expression in general English. We cannot all be Churchills or Bacons, but we can raise our standards. Vexatious expressions and customs in medical writing fall into a number of different categories which I shall list, and of which I shall give examples.

Solecisms represent violations of the rules of grammar and logic. An outstanding example is the term that has grown on us like a cancer in recent years—"insulin-dependent diabetes mellitus." One can accept that the diabetic patient is dependent on insulin, but the disease, never! The contrary is the case, if the relationship is to be signaled.[1] "Data is" has crept into American usage and is considered acceptable by some.[2] Surprisingly, an expert panel of modern writers[3] voted against this usage by only a slim margin of 51 to 49 percent. Yet to the trained ear this Latin plural of "datum" requires a plural verb. In Great Britain, the expression "data is" qualifies as a solecism.[4] Unique means "only one exists" and must not be qualified.[4] The commonly heard "more unique" or "very unique" might qualify as a solecism.

Barbarisms may be defined as use of nonexistent words or expressions. A common example is "the patient was anticoagulated" instead of "given anticoagulants." In heaven's name, why must we say a "repeat test or study? Why not "repeated" or "another" or "a second"? A "repeat" electrocardiogram smacks of jargon or colloquialism and can even qualify as a barbarism.

Dangling expressions: Like the rest of America, medicine has fallen prey to the lure of dangling expressions. One is the ubiquitous "hopefully": "Hopefully, the solution will be found." But what does hopefully modify? Why not, "Hopefully, we work for a solution" or "It is hoped that a solution will be found"? The panel of modern writers[3] voted against this usage of *hopefully* 76 to 24 percent. Worse by far is the dangling participle: "Using the aforementioned method, the studies were carried forward." Impossible! What does *using* refer to? It should be, instead, "We carried the studies forward using the aforementioned method." Another example: "Based on the data, we took action." "We" are not based on the "data"; one might say, "Basing our decision on these data . . ." This matter is covered in Strunk and White's seventh rule of style[5]: "A participial phrase at the beginning of a sentence must refer to the grammatical subject."[5]

Faulty definitions: In many instances, expressions are misused because of misunderstanding of their meaning, especially when there is close resemblance to another word. "Mitigate" is commonly substituted for *militate,* as in "This observation 'mitigates' against that conclusion." "Imply" and "infer" are often reversed.[5] In the area of medical science, we find "parameter" used ad nauseam. The expression should be "variable." A parameter is a variable in a series of equations, often of an assigned value. "Gradient" does not mean "a pressure difference," although it is so used almost universally. It means a rate of change of difference.

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Prolixity and verbosity: In medical writing as elsewhere, we often fail to take enough time to prune our papers to the choice, essential words. One author said, "If I had more time, I would write you a shorter letter." Or to quote Thoreau,[6] "Not that the story need be long, but it will take a long while to make it short." Generally, the shorter way of saying a thing is also better (Strunk and White's rule 13).[5] Some expressions in themselves are verbose; "at this point in time" is one example. Why not "now" or "at present"? Why "reported on" instead of "reported"?

Medical writing is also full of unnecessarily stilted or pompous expressions, often polysyllabic. Many of these are trite or clichés, and fall wearily on the jaded ear. For example, why the preference for "prior to" rather than "before,"[7] or "subsequently" instead of "later," "next" or "afterward"? Harper's dictionary[3] lists "prior to"as stilted, unless referring to an event of great significance and duration. Is "ambulate" really better than "walk" or "ingest" superior to "eat"? Does "encounter" sound better than "meet with," or "assessment" better than "evaluation"? "Encounter" suggests the meeting by accident of two or more important persons or groups, while "assessment," to my mind, conjures up a picture of a visit from the IRS tax man. "Mandatory" sounds imperative and pompous; "necessary" or "essential" is better. "Noted" sounds more hackneyed than "saw" or "observed." Is to be "cognizant of" or "aware of" really better than to "know"? Is "expired" (which may also mean "exhaled") really better than "died"? To "herald" a disease seems overly dramatic; why not "foretell"? "Protean" should probably be buried under the sea with Proteus, the monster.

We are also guilty of errors in syntax and faults in logic. How often is a graph, an electrocardiogram, a radiogram or a line referred to as "this patient"? Illogical comparisons are often made: "The patient's face resembled acromegaly," instead of "was characteristic of acromegaly"; or, even worse, "The patient had a temperature" (this must be true all the way down to cessation of motion of matter at −273° C); or, horrors, "The patient fibrillated," meaning "He had atrial fibrillation." I have a mental picture of a patient with diffuse muscular fasciculation over all of his body.

Finally, I must make a thrust in the direction of some common medical expressions that are not incorrect, but nevertheless detract from the quality of writing and the spoken word. A highly unnecessary medical variation on customary usage is the use of therapeutic "régime" instead of "regimen." A régime refers to a mode or system of government. Although *régime* in French may refer to a diet or regimen,[8] I see no reason, our dictionaries to the contrary,[9] to sanction a use of this word in medicine to replace the word used in general English. "Presently" does not mean "now" but "in a little while." The panel[3] voted 82 to 18 percent against "presently" in the former meaning. Fowler[4] points out that "presently" is unnecessary in this sense when we have "now," "at present" and "currently." The use of "males" to mean men and "females" to mean women, although technically correct, smacks of an unpleasant depersonalization. "Male" and "female" are better applied to animals. "Compatible" is overused and unnecessarily evasive: "This test or finding is compatible with a diagnosis of tuberculosis." In the sense of "not inconsistent with," this statement could be made about the majority of medical tests, findings or procedures. If what is meant is "suggestive of," why not say so?

In the first paragraph of this essay, I touched on the value of better, clearer, more precise writing. It is true that most medical writers are intelligent and well schooled; their message is usually understood even though the presentation is second-rate. Yet, a paper is more likely to be read and reread, more likely to be understood and remembered and more likely to be quoted when it is well done. Finally, there is a sense of pleasure and satisfaction in reading the scholarly essay, a feeling that comes not from the pedestrian, the commonplace, the clichés, the colloquialisms borrowed from hospital corridor conversations and ward round jargon. Let us forsake the conventional and the hackneyed polysyllabic expressions, and add a bit of sparkle to what we have to say by making better use of the precise tool our forebears have bequeathed us.

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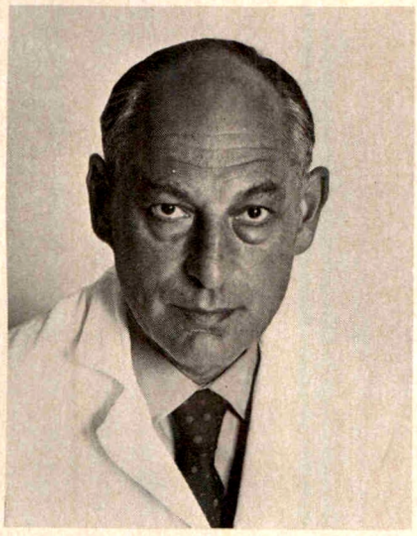
PRESIDENT'S PAGE:

Should We Reduce Graduate Cardiovascular Training Programs?: Readers Opinions



Borys Surawicz, MD, FACC

The following letters have been excerpted from responses to the Presidents' Page of April 1979 (Am J Cardiol 44: 870–871, 1979).

I absolutely agree with your concern, and agree in general with your final quote . . . .

Louis Cohen, MD
Department of Medicine
Section of Cardiology
University of Chicago
Chicago, Illinois

* * *

. . . I agree with you 100% in your explanation of the problem, and I support any action that you may take.

F. L. Lummus, MD
Internal Medicine Associates
Tupelo, Mississippi

* * *

. . . Your carefully reasoned appraisal of evaluations of graduate cardiovascular training programs is timely and appropriate. I trust it will help mobilize professional attitudes and opinions towards the realities of the magnitude of cardiovascular disease and the continuing need for an adequate number of well trained cardiologists to meet the needs of the public for excellence in medical care . . .

Robert A. Bruce, MD
Co-Director, Division of Cardiology
University of Washington
Seattle, Washington

* * *

. . . As a practicing cardiologist, it has been my very recent impression that more and more people trained to do invasive procedures, such as coronary arteriography, are being dumped into the practice situation . . . . As I see it, the more of these people who are dumped into the practice the fewer procedures there will be for each one and the more risky the procedure may become.

. . . I realize that more data are necessary in order to be totally sure of what the situation should be, but I don't think there is any question at the moment that there are too many invasive cardiologists being produced.

. . . I think the training positions should be limited and the competition for them should be great.

David H. Jackson, MD
Brookwood Medical Center
Birmingham, Alabama

* * *

. . . I would certainly not demean or attempt to restrict the desire of those wishing to go on into the subspecialties, but on the other hand I think that a great deal more must be done in broadening the perspective of the general internist and a great deal more emphasis must be placed on family counseling and family advice and less on repeated consultations in the various fields . . . .

. . . I do not pretend to know the answers, but certainly we cannot go on the way we are. Costs, risks, abusive technology and procedures, consultations seem to be rising at a tremendous rate and I see no significant effective efforts at control . . . .

. . . I have a different point of view and perhaps the academic world and the actual clinical practice of medicine as it really is in America are simply two different worlds apart. I hope that is not true and that something can be done to bring them together more effectively for America, its people who deserve better, and for medicine.

John F. Finnegan, MD
Consultation, Internal Medicine
Washington, D.C.

* * *

. . . I have witnessed the pressures of private practice regarding success or failure lead to creating demand by proffering more and more procedures each ostensibly giving the doctor a more precise diagnosis . . . . Somehow the newer procedures offer a renewed hope of increasing precision and taking away the subjective in favor of the more objective. Meanwhile, the cost of these new investigative appliances are continuing to drive the cost of medical care out of sight.

So where does the utilization of new procedural equipment connect with having less trained subspecialties? Well, if

there were fewer subspecialists and they didn't have the monetary pressures of keeping up with the procedural income to make their time cost effective, there would be need for fewer gadgets and those that are needed would be better utilized.

. . . I believe the shortage of clinical investigators is being cared for by the glut of physician subspecialty fellowships . . . like the fuel in a nuclear reactor, when the fellow's time has come he must be disposed of and usually this is into the realm of private practice. Thus, the spinoff of the physician glut in regards to the subspecialist will be determined by the total number of fellowships created. With each medical center working feverishly to be heard from and some of which having already created an empire within whose bounds no one actually knows just how many fellowship slots are contained, there is little doubt in my mind that there will be plenty of subspecialty supply for who knows how much demand.

I truly believe Doctor Surawicz's comments are well intentioned but favor taking a contrary stand to his belief that the logic of supply and demand should be allowed to be operative in the field of Medicine. Rather, I think the time has come that we begin making the tough decisions of basing our medical school enrollment and subspecialty fellowship slots on projected needs. We can always err on the side of having a few too many to keep competition alive, but still prevent the glut which could destroy Medicine as we know it today. By creating a wholesale atmosphere of too many physicians the pressure of success will in reality continue to force the competitors to create demand by offering more procedures. Eventually, someone outside the medical community will attempt to set things right. I prefer to have this be an inside job . . . .

Shields Stutts, MD
8818 Sagebrush Lane
San Antonio, Texas

29TH ANNUAL SCIENTIFIC SESSION

AMERICAN COLLEGE OF CARDIOLOGY

HOUSTON, TEXAS MARCH 9–13, 1980

CALENDAR OF EXTRAMURAL PROGRAMS

The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the National Committee of Continuing Education assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The National Program Committee for Continuing Medical Education of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Leonard S. Dreifus, MD, FACC
Chairman, Continuing Education Committee for Extramural Programs

Programs and faculty are subject to change. For further information write Registration Secretary, Extramural Programs Department, American College of Cardiology, Heart House, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

NOVEMBER 1979 THROUGH APRIL 1980

To be arranged individually — **Preceptorships in Cardiology.** Arthur Seizer, FACC, director, Pacific Medical Center, San Francisco, CA

To be arranged individually — **Preceptorships in Cardiology.** Jules Constant, FACC, director. Buffalo General Hospital, Buffalo, NY

NOV. 5–14 — **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC and James E. Crockett, FACC, directors. Rancho Santa Fe Inn, Rancho Santa Fe, CA

DEC. 2–5 — **Coronary, Hypertensive, Valvular, and Myocardial Heart Diseases: The Multi-disciplinary Approach.** William C. Roberts, FACC, director. Williamsburg Conference Center, Williamsburg Lodge, Williamsburg, VA

DEC. 7–9 — **Advances in Heart Disease 1980.** Dean T. Mason, FACC, director. Fairmont Hotel, San Francisco, CA

DEC. 12–14 — **Cross-Sectional Echocardiography vs. Cardiac Nuclear Imaging.** Joel Morganroth, FACC, director. Fairmont Hotel, Philadelphia, PA

DEC. 14–16 — **Twelfth Annual Cardiovascular Symposium: Clinical Decisions in Cardiovascular Disease.** Henry I Russek, FACC, director. Sheraton Centre, New York, NY

1980

JAN. 14–18 — **Eleventh Annual Cardiovascular Conference at Snowmass.** John H. K. Vogel, FACC, director and Bruce C. Paton, FACC, co-director. Snowmass Resort, Snowmass, CO

JAN. 15 — **Coronary Artery Disease: Diagnosis and Treatment.** William C. Sheldon, FACC and J. Kent Trinkle, directors. Convention Center, San Antonio, TX

JAN.31–FEB. 2 — **Fundamentals of Echocardiography—An Introductory Course for Clinicians.** Joseph K. Perloff, FACC, director and Pravin M. Shah, FACC and John S. Child, FACC, co-directors. Century Plaza Hotel, Los Angeles, CA

FEB. 13–15 — **Cardiac Diagnosis: Reappraisal of Established Techniques and the Place for New Techniques.** Ralph Shabetai, FACC, John Ross, Jr., FACC, Gabriel Gregoratos, FACC and Joel S. Karliner, FACC, directors. Vacation Village Hotel, San Diego, CA

MAR. 24–28 — **Thirteenth Annual Seminar. Electrocardiographic Interpretation of Complex Arrhythmias: A Physiological Approach.** Charles Fisch, FACC and Douglas P. Zipes, FACC, directors. Indiana University Medical Center, Indianapolis, IN

APR. 7–16 — **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC and James E. Crockett, FACC, directors. Rancho Santa Fe Inn, Rancho Santa Fe, CA

APR. 10–13 — **Current Concepts and Advances in Diagnosis, Management and Prevention of Cardiac and Cardiopulmonary Diseases.** James S. Forrester, FACC, director. Los Angeles, CA

APR. 14–18 — **Consultant's Course in Cardiology.** Michael V. Herman, FACC, director and Louis E. Teichholz, FACC, Richard Gorlin, FACC and Simon Dack, FACC, co-directors. Mt. Sinai Medical Center, New York, NY

APR. 16–18 — **Vectorcardiography—Basic Workshop.** Alberto Benchimol, FACC, director. Scottsdale Hilton Hotel, Scottsdale, AZ

APR. 21–23 — **Practical Cardiology for the Family Physician.** Robert S. Eliot, FACC, director. Marriott Hotel, San Antonio, TX

APR. 24–26 — **The Pathology of Congenital Heart Disease.** Maurice Lev, FACC, director. Palmer House, Chicago, IL

APR. 25–27 — **New Concepts in Clinical Electrocardiography.** William J. Mandel, FACC and Irwin Hoffman, FACC, directors. Beverly Hilton Hotel, Beverly Hills, CA

LEARNING CENTER: PROGRAM CALENDAR

The American College of Cardiology's newest department, the Learning Center, located at the College's Bethesda Maryland headquarters, began operations in October 1977 with the offering of its first continuing medical education program for physicians with a specialty or an interest in cardiovascular medicine. The purpose of the Learning Center is to support the professional commitment to quality patient care by providing a new standard of excellence in cardiovascular continuing education. For additional information concerning the programs listed below or for a complete schedule of programs through July 1980, contact Program Coordinator, Learning Center, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20014. Telephone (301) 897-5400.

NOVEMBER 1979 THROUGH MAY 1980

Month/Dates	Program Director	Title of Program
Nov. 1–3	Barrie Levitt, MD	Cardiovascular Therapeutics
Nov. 28–30	William W. Parmley, MD	Noninvasive Cardiovascular Procedures: Principles and Clinical Applications
Jan. 21–23	William C. Roberts, MD	Congenital Heart Disease: The Multidisciplinary Approach
Jan. 28–30	Gottlieb Friesinger, MD	Surgery in Ischemic Heart Disease
Feb. 6–8	Bertram Pitt, MD	Nuclear Cardiology
Feb. 11–13	Melvin L. Marcus, MD	New Approaches to the Short and Long Term Treatment of Myocardial Infarction
Feb. 18–20	Roger A. Winkle, MD	Antiarrhythmic Therapy: Current Status and Future Promise
March 24–26	John A. Mantle, MD	Quality Assurance and Management for Cardiovascular Nurses
March 27–29	John Spittell, MD	Peripheral Vascular Disease
April 9–11	Victor Parsonnet, MD	Current Concepts in Pacing
April 14–16	Keith Cohn, MD	Exercise Testing
April 21–23	Nanette Wenger, MD	Rehabilitation of the Cardiac Patient
April 28–30	Pravin M. Shah, MD	M-Mode and 2-Dimensional Echocardiography: Current Status and Future Promise
May 1–3	Daniel S. Berman, MD	Nuclear Cardiology
May 5–7	Robert G. Tancredi, MD	Pulmonary, Renal and Electrolyte Considerations in Cardiovascular Disease
May 12–14	Louis Lemberg, MD	CCU Update for Nursing Supervisors
May 19–21	Arthur E. Weyman, MD	Cross-Sectional Echocardiography
May 28–30	Elliot Rapaport, MD	Cardiology for the Consultant

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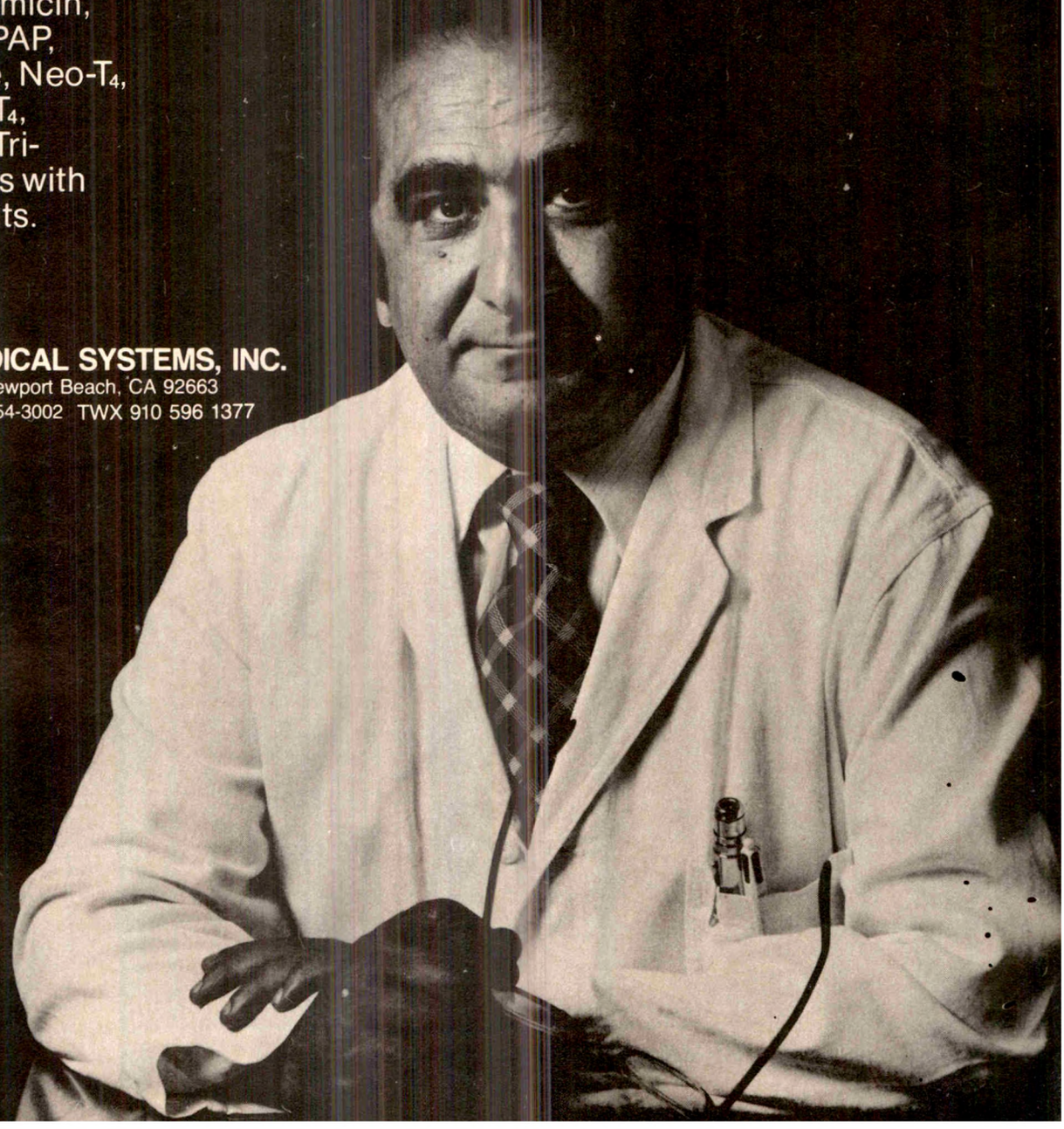

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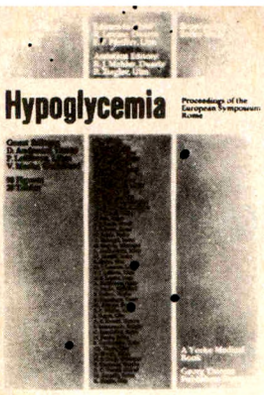

One of the Most Frequently Overdiagnosed Diseases!

■ *Here at last is an objective study of essential reactive hypoglycemia . . . definition, recognition, pathology, etiology, and treatment.*

Editors:

D. Andreani, MD, Prof. of Clinical Endocrinology, Univ. of Rome
P. Lefèbvre, MD, Dept. of Medicine, University of Liège
V. Marks, DM, Prof., Dept. of Biochemistry, Univ. of Surrey

This European (Rome) Symposium was the first free interchange of ideas among scientists in the various medical disciplines—physiology, internal medicine, endocrinology, clinical biochemistry, etc.—necessary to the understanding, diagnosis and treatment of hypoglycemia. The concentration was on the various aspects of insulin-producing tumors and the vexed question of essential reactive hypoglycemia. Special attention was given to the widespread misinterpretation of laboratory data relating to the prolonged oral glucose test which has resulted in the erroneous belief that "millions suffer from hypoglycemia."

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KATO®
(potassium chloride for oral solution)

20 mEq (1.5 g. KCl)

Prescribing Information

DESCRIPTION:
Spray-dried tomato powder containing 20 mEq potassium (equivalent to 1.5 g. KCl) per 6 grams powder (one dose) with natural and synthetic flavors, spices and colors. Benzoic acid and potassium benzoate added as preservatives. When reconstituted as directed, makes a pleasantly flavored, low sodium tomato juice drink. Each daily dose (2 packets) contains less than 10 mg. sodium.

INDICATIONS:
The prevention or correction of potassium deficit, particularly when accompanied by hypochloremic alkalosis in conjunction with thiazide diuretic therapy, in digitalis intoxication, or as the result of long-term corticosteroid therapy, low dietary intake of potassium, or excessive vomiting or diarrhea.

CONTRAINDICATIONS:
Potassium is contraindicated in severe renal impairment involving oliguria, anuria or azotemia; in untreated Addison's disease, familial periodic paralysis, acute dehydration, heat cramps, hyperkalemia from any cause. Potassium chloride should not be employed in patients receiving potassium-sparing agents such as aldosterone antagonists and triamterene.

PRECAUTIONS:
KATO is a concentrate and should be taken only after reconstituting with water as directed. This preparation, like other potassium supplements, must be properly diluted to avoid the possibility of gastrointestinal irritation. Do not use in patients with low urinary output or renal decompensation. Administer with caution; it is impossible to assess accurately the daily dose required. Excessive dosage may result in potassium intoxication. Frequent checks of the clinical status of the patient, ECG and/or plasma potassium level should be made. High plasma concentrations of potassium ion may cause death through cardiac depression, arrhythmias or arrest. Use with caution in patients with cardiac disease.

ADVERSE REACTIONS:
Vomiting, diarrhea, nausea, and abdominal discomfort may occur. Gross overdosage may produce signs and symptoms of potassium intoxication: mental confusion, listlessness, paresthesia of the extremities, weakness and heaviness of legs, flaccid paralysis, hyperkalemia, ECG abnormalities, fall in blood pressure, cardiac arrhythmias and heart block. The characteristic changes in the ECG are disappearance of the P wave, widening and slurring of QRS complex, changes of the S-T segment, tall peaked T waves, etc.

TOXICITY:
Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

TREATMENT OF HYPERKALEMIA:
1. Dextrose solution 10% or 25% containing 10 units of crystalline insulin per 20 g. dextrose, given I.V. in a dose of 300cc to 500cc in an hour. 2. Adsorption and exchange of potassium using sodium or ammonium cycle cation exchange resin, orally or as retention enema. 3. Hemodialysis or peritoneal dialysis. 4. Elimination of potassium-containing foods and medicaments. Warning: Digitalis toxicity can be precipitated by lowering the plasma potassium concentration too rapidly in digitalized patients.

ADMINISTRATION AND DOSAGE:
Mix with water to make a pleasant tomato juice drink. Each 6 gram unit dose packet provides 20 mEq of potassium. Usual adult dose—1 packet of KATO mixed with about 2 ounces of water twice daily—supplies 40 mEq potassium per day. Take with meals or follow with ½ glass of water. Larger doses may be required, but should be administered under close supervision because of the possibility of potassium intoxication.

HOW SUPPLIED:
Cartons of 30 and 120 6 gram unit dose packets, 20 mEq each.

02-488-30
1-79

SYNTEX

SYNTEX PUERTO RICO, INC.
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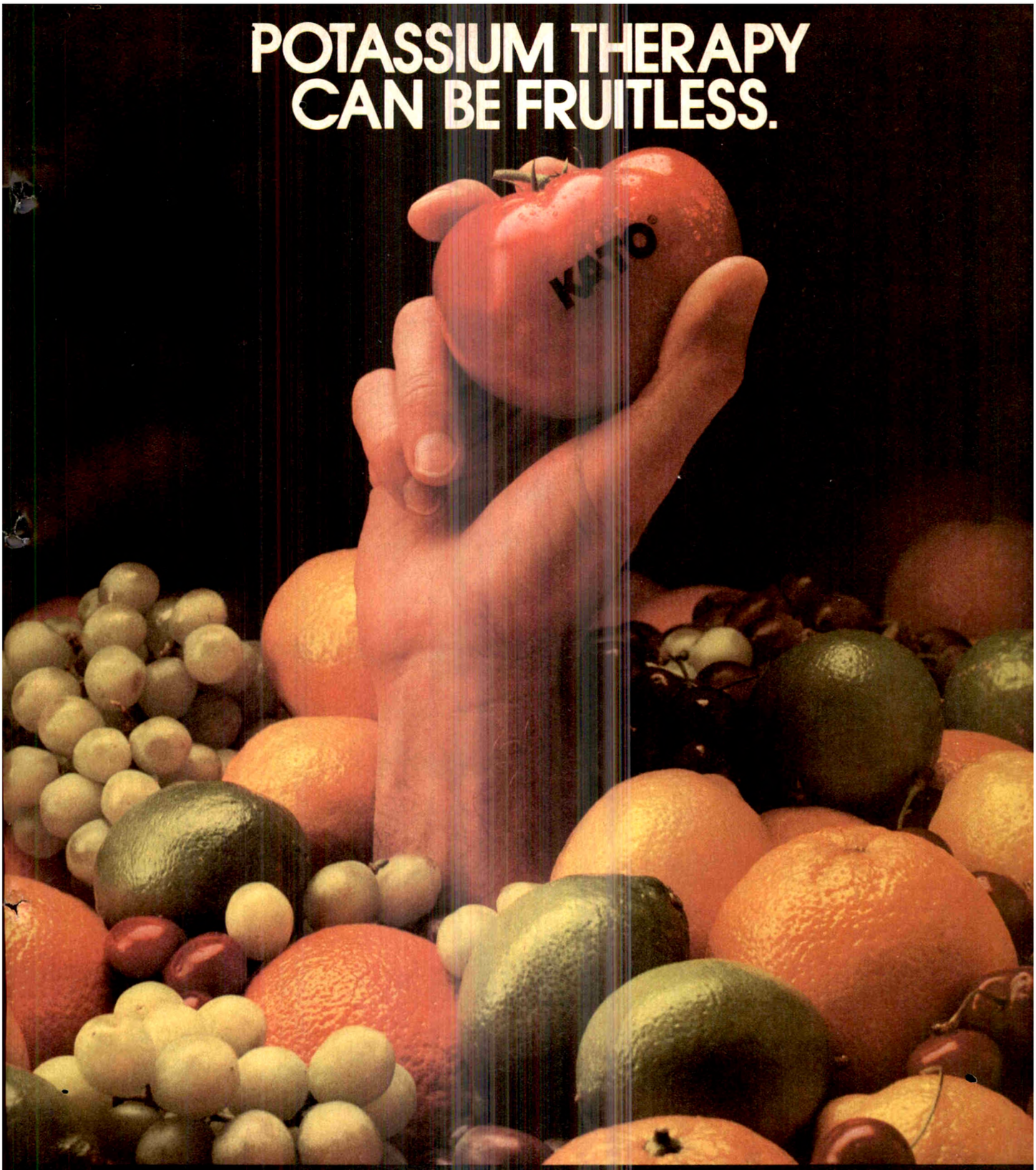
POTASSIUM THERAPY CAN BE FRUITLESS.



Trying to smother the taste of potassium with sweet fruit flavorings never seems to work very well. It's like pouring salt straight into your orange juice—and just about as undrinkable for many patients. That's when a matter of taste becomes a problem of compliance.

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(QUINIDINE GLUCONATE TABLETS)

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TABLETS, 330 mg

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*The quantity of drug and frequency of administration needed to achieve desired clinical results must be determined for each patient.
†Red Book, 1979.

DuraQuin®
(QUINIDINE GLUCONATE TABLETS)

sustained-release tablets, 330 mg

Brief summary of prescribing information
DURAQUIN® (quinidine gluconate tablets) Sustained Release

CLINICAL PHARMACOLOGY: In clinical studies, single doses of Duraquin produced a mean maximum plasma level at 2 hours which was maintained for 12 hours. This broad plateau indicates slow, continuous absorption from the gastrointestinal tract.

In multiple dose studies, administration of Duraquin tablets, 660 mg every 12 hours, produced steady state (equilibrium) plasma levels shortly after 24 hours. The average quinidine plasma levels (Cramer and Isaksson assay[1]) were 0.81 mcg/ml and the mean peak levels were 1.16 mcg/ml in a group of normal male subjects weighing 75 Kg. Following the last dose at steady state, quinidine plasma levels decreased at an approximate rate of 50% in 10 hours. This compares to the expected plasma half-life of 6.3 hours for quinidine sulfate tablets, USP.

Therapeutic and toxic effects coordinate better with plasma levels than with dosage. While therapeutic levels of 3 to 6 mcg/ml with a range of 1.5 to 9 mcg/ml have been reported, these values are based on peak plasma levels determined by the less specific Edgar and Sokolow assay[2]. This procedure yields quinidine levels averaging 22% higher than the Cramer and Isaksson assay. Plasma levels vary considerably in patients receiving identical doses. Therefore, it is advisable to adjust the dosage by monitoring plasma quinidine levels.

INDICATION: Duraquin tablets are indicated for the prevention of premature atrial, nodal, or ventricular contractions. They are also indicated for the maintenance of normal sinus rhythm following spontaneous reversion or electrical conversion of atrial, nodal, or ventricular tachycardia, atrial flutter and fibrillation (either paroxysmal or chronic).

[1]Cramer, G. and Isaksson, B. Quantitative Determination of Quinidine in Plasma. Scandinavian J. Clin. & Lab. Investigation 15, 553, 1963.
[2]Edgar, A.L. and Sokolow, M. Experiences with the Photofluorometric Determination of Quinidine in Blood. J. Lab. Clin. Med. 36, 478, 1950.

CONTRAINDICATIONS: 1. History of hypersensitivity to quinidine manifested by thrombocytopenia, skin eruption, febrile reactions, etc.
2. Complete A-V block.
3. Complete bundle branch block or other severe intraventricular conduction defects exhibiting marked QRS widening or bizarre complexes.
4. Myasthenia gravis.
5. Arrhythmias associated with digitalis toxicity.

WARNINGS: 1. (a) In the treatment of atrial fibrillation with rapid ventricular response, ventricular rate should be controlled with digitalis glycosides *prior* to administration of quinidine.
(b) In the treatment of atrial flutter with quinidine, reversion to sinus rhythm may be preceded by progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely high ventricular rate. This potential hazard may be reduced by digitalization prior to administration of quinidine.

Recent reports have described increased, potentially toxic, digoxin plasma levels when quinidine is administered concurrently. When concurrent use is necessary, digoxin dosage should be reduced and plasma concentration should be monitored and patients observed closely for digitalis intoxication.
2. Quinidine cardiotoxicity may be manifested by increased PR and QT intervals, 50% widening of QRS, and/or ventricular ectopic beats or tachycardia. Appearance of these toxic signs during quinidine administration mandates immediate discontinuation of the drug, and/or close clinical and electrocardiographic monitoring. Note: Quinidine effect is enhanced by potassium and reduced in the presence of hypokalemia.
3. "Quinidine Syncope" may occur as a complication of long-term therapy. It is manifested by sudden loss of consciousness and ventricular arrhythmias with bizarre QRS complexes. This syndrome does not appear to be related to dose or plasma levels but occurs more often with prolonged QT intervals.

Brief summary continued on following page.

PD-JA-2299-2-P(11-79)

PARKE-DAVIS

PARKE-DAVIS
Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA

Duraquin®
(QUINIDINE GLUCONATE TABLETS) sustained-release tablets, 330 mg

Brief summary continued from previous page.

4. Because quinidine antagonizes the effect of vagal excitation upon the atrium and the A-V node, the administration of parasympathomimetic drugs (choline esters) or the use of any other procedure to enhance vagal activity may fail to terminate paroxysmal supraventricular tachycardia in patients receiving quinidine.
5. Quinidine should be used with extreme caution in:
a) The presence of incomplete A-V block, since a complete block and asystole may result. Quinidine may cause unpredictable abnormalities of rhythm in digitalized hearts. Therefore, it should be used with caution in the presence of digitalis intoxication (see 1. (b) above).
b) Partial bundle branch block.
c) Severe congestive heart failure and hypotensive states due to the depressant effects of quinidine on myocardial contractility and arterial pressure.
d) Poor renal function, especially renal tubular acidosis, because of the potential accumulation of quinidine in plasma leading to toxic concentrations.

PRECAUTIONS:

1. Test Dose—A preliminary test dose of a single tablet of quinidine *sulfate* should be administered prior to the initiation of the sustained release gluconate to determine whether the patient has an idiosyncrasy to the Quinidine molecule.

2. Hypersensitivity—During the first weeks of therapy, hypersensitivity to quinidine, although rare, should be considered (eg, angioedema, purpura, acute asthmatic episode, vascular collapse).

3. Long-Term Therapy—Periodic blood counts and liver and kidney function tests should be performed during long-term therapy and the drug should be discontinued if blood dyscrasias or signs of hepatic or renal disorders occur.

4. Large Doses—ECG monitoring and determination of plasma quinidine levels are recommended when doses greater than 2.5 g/day are administered.

5. Usage in Pregnancy—The use of quinidine, in pregnancy, should be reserved only for those cases where the benefits outweigh the possible hazards to the patient and fetus.

6. Nursing Mothers—The drug should be used with extreme caution in nursing mothers because the drug is excreted in breast milk.

7. General—In patients exhibiting asthma, muscle weakness, and infection with fever *prior* to quinidine administration, hypersensitivity reactions to the drug may be masked.

DRUG INTERACTIONS:

1. Caution should be used when quinidine and its analogs are administered concurrently with coumarin anticoagulants. This combination may reduce prothrombin levels and cause bleeding.
2. Quinidine, a weak base, may have its half-life prolonged in patients who are concurrently taking drugs that can alkalize the urine, such as thiazide diuretics, sodium bicarbonate, and carbonic anhydrase inhibitors. Quinidine and drugs which alkalize the urine should be used together cautiously.
3. Quinidine exhibits a distinct anticholinergic activity in the myocardial tissues. An additive vagolytic effect may be seen when quinidine and drugs having anticholinergic blocking activity are used together. Drugs having cholinergic activity may be antagonized by quinidine.
4. Quinidine and other antiarrhythmic agents may produce additive cardiac depressant effects when administered together.
5. Quinidine interaction with cardiac glycosides (digoxin); See WARNINGS.
6. Antacids may delay absorption of quinidine but appear unlikely to cause incomplete absorption.
7. Phenobarbital and phenytoin may reduce plasma $t_{1/2}$ of quinidine by 50%.
8. Quinidine may potentiate the neuromuscular blocking effect in ventilatory depression of patients receiving decamethonium, tubocurare, or succinylcholine.

ADVERSE REACTIONS: Symptoms of cinchonism (ringing in the ears, headache, disturbed vision) may appear in sensitive patients after a single dose of the drug.

Gastrointestinal: The most common side effects encountered with quinidine are referable to this system. Diarrhea frequently occurs, but it rarely necessitates withdrawal of the drug. Nausea, vomiting, and abdominal pain also occur. Some of these effects may be minimized by administering the drug with meals.

Cardiovascular: widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms including ventricular tachycardias and fibrillation; paradoxical tachycardia, arterial embolism and hypotension.

Hematologic: acute hemolytic anemia, hypoprothrombinemia, thrombocytopenic purpura, agranulocytosis.

CNS: headache, fever, vertigo, apprehension, excitement, confusion, delirium and syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, photophobia, diplopia, night blindness, scotomata); optic neuritis.

Dermatologic: cutaneous flushing with intense pruritus.

Hypersensitivity reactions: angioedema, acute asthmatic episode, vascular collapse, respiratory arrest.

DOSAGE AND ADMINISTRATION: Dosage should be titrated to give the desired clinical effect, e.g., elimination of paroxysmal rhythm or reduction in premature contractions (See CLINICAL PHARMACOLOGY). This will often require prolonged ambulatory ECG monitoring, as hour-to-hour variability renders brief ECG recordings unreliable. When doses larger than 2.5 g/day are used, quinidine blood levels should be monitored, if possible, and serial ECGs should be followed (See WARNINGS and PRECAUTIONS).

For prevention of premature contractions and maintenance of normal sinus rhythm following spontaneous reversion or electrical conversion, the usual dosage is from 330 mg to 660 mg every eight hours, most patients requiring the higher dose.

In elderly patients, and in patients in the lower end of the normal weight range, plasma quinidine determinations should be considered. Dosage adjustments may be required.

OVERDOSAGE: Cardiotoxic effects of quinidine may be reversed in part by molar sodium lactate; the hypotension may be reversed by vasoconstrictors and by catecholamines (since the vasodilation is partly due to alpha-adrenergic blockade).

HOW SUPPLIED: N 0071-0850 (P-D 850) Duraquin (quinidine gluconate tablets) 330-mg tablets are supplied in bottles of 100 tablets.

AHFS Category 24:04

YD

PARKE-DAVIS

Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA

Brief Summary of Prescribing Information

Indications and Usage: Symptomatic relief of anxiety, tension, agitation, irritability and insomnia associated with anxiety neuroses and transient situational disturbances; anxiety associated with depressive symptoms and as a treatment of symptoms of anxiety if such symptoms are a significant feature of functional or organic disorders, particularly gastrointestinal or cardiovascular.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients on lorazepam not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation.

Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions.

Observe usual precautions with impaired renal or hepatic function.

Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component.

Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg kg day. No effect dose was 1.25mg/kg/day (approximately 6 times the maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatric patients requires caution and frequent monitoring for symptoms of upper G.I. disease.

Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug.

In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind that multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring of vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® IV for (lorazepam) Anxiety

Dosage: **Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.**

How Supplied: **0.5, 1.0 and 2.0mg tablets.**

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Philadelphia, PA 19101

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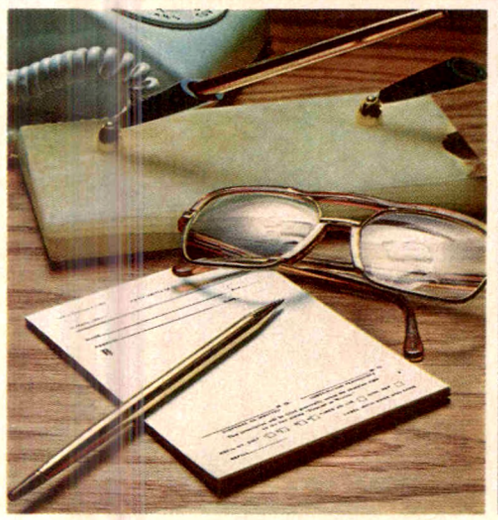
Why one benzodiazepine and not another?

Are you concerned about long-acting metabolites? Many clinicians, as well as pharmacologists, are beginning to draw attention to this problem (see New England Journal of Medicine, April 5, 1979).

In contrast to some older benzodiazepines, Ativan (lorazepam) does not give rise to long-lasting active metabolites. As with all benzodiazepines, you should follow the usual precautions concerning co-administration with other CNS depressants and warn your patients against operating dangerous machinery and motor vehicles.

However, it is noteworthy that Ativan showed no clinical evidence of accumulation even when given in high doses over periods up to 6 months. The half-life of free lorazepam is about 12 hours; steady-state serum levels are attained in 2-3 days. Comparable data for diazepam: 20-50 hours and at least 7-10 days. (The pharmacokinetic profile of a drug can define such characteristics as absorption, distribution, metabolism and elimination but cannot, at present, be directly related to its therapeutic effectiveness.)

Ativan has a convenient b.i.d. or t.i.d. dosage schedule; it is compatible with a long list of other medications and, of course, it is a highly effective anxiolytic agent, as established in numerous nationwide, double-blind, controlled evaluations in thousands of patients.



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For prolonged prophylactic action, with improved left ventricular function

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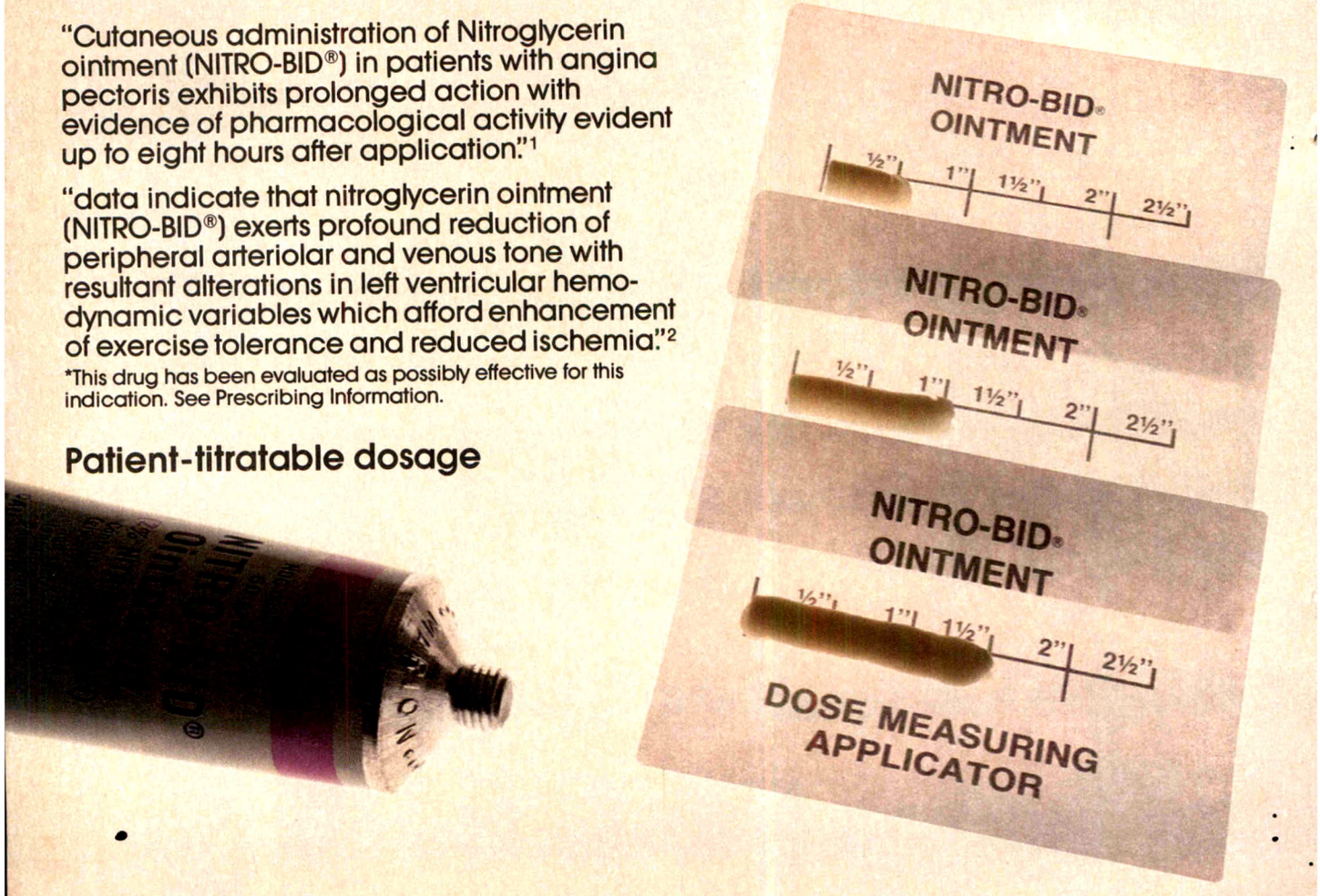
"data indicate that nitroglycerin ointment (NITRO-BID®) exerts profound reduction of peripheral arteriolar and venous tone with resultant alterations in left ventricular hemodynamic variables which afford enhancement of exercise tolerance and reduced ischemia."[2]

*This drug has been evaluated as possibly effective for this indication. See Prescribing Information.



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Description: Nitroglycerin 2% (glyceryl trinitrate) and lactose in special lanolin-petrolatum base.

Action: Nitroglycerin is continuously absorbed through the skin into the circulation, thus exerting prolonged vasodilator effect.

Indications: "Possibly" Effective: Prevention and treatment of angina pectoris attacks, especially at night.

Precautions: Headache is a sign of overdosage, so reduce dosage. Occasionally elderly patients may develop postural hypotension with faintness upon suddenly arising. May be contraindicated in patients with marked anemia, increased intraocular pressure or increased intracranial pressure. Don't use in patients with a known idiosyncrasy to nitrites.

Dosage and Administration: Usual dose is 1-2 inches, as squeezed from tube. Some patients require 4-5 inches. To determine optimal dosage, start with ½ inch, increase dose ½ inch at a time until headache occurs, then drop back to largest dose which doesn't cause headache. Apply to desired skin area with Dose Measuring Applicator. DO NOT USE FINGERS. Spread in thin, uniform layer. May be applied every 3-4 hours if necessary. To stop treatment of anginal patients, gradually reduce dosage and frequency of application over period of 4-6 weeks to prevent characteristic nitroglycerin withdrawal reactions.

Caution: Federal law prohibits dispensing without prescription.

Consult full product disclosure before prescribing.

References:

1. Davidov M, Mroczek W: The effect of nitroglycerin ointment on exercise capacity in patients with angina pectoris. Presented at American College of Pharmacology meeting, Washington DC, April 1977.

2. Awan NA, Miller RR, Maxwell KS, et al: Cardiocirculatory and antianginal actions of nitroglycerin ointment. Chest 73:14-18 (Jan) 1978.

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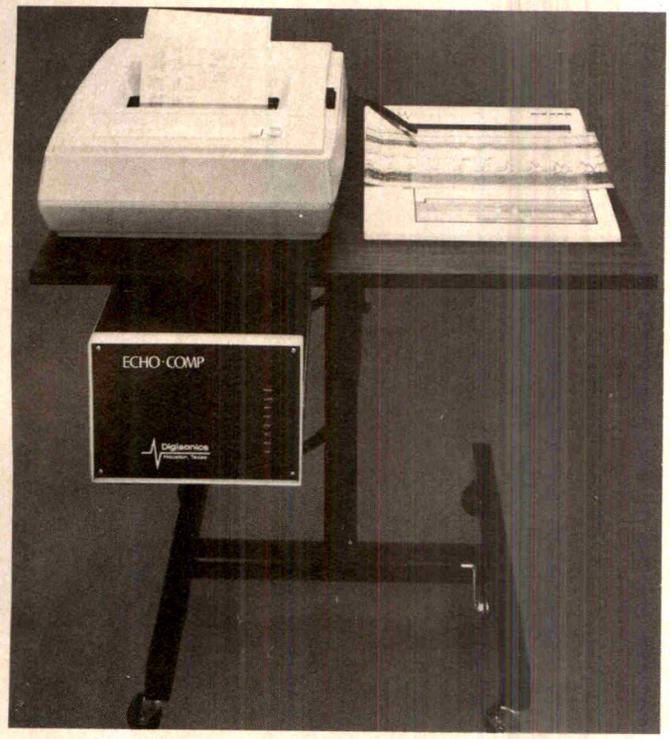

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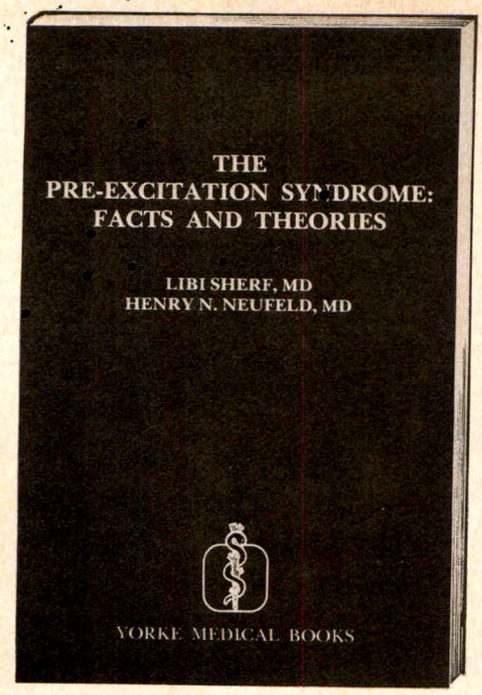

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THE PRE-EXCITATION SY FACTS AND THE

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Every Cardiologist, Internist, Pediatrician, Surgeon — Indeed, *Every Physician* — Should Have a Good Basic Knowledge of The Pre-excitation Syndrome. Here Are Just a Few Reasons Why This is so Essential:

- ☐ ⅓ of all pre-excitation cases are misdiagnosed.
- ☐ 5% to 10% of all tachycardias in adults are produced by pre-excitation.
- ☐ In ½ of all infants under 10 months of age with life-threatening tachycardias, the tachycardias are actually secondary to pre-excitation.
- ☐ ⅓ to ½ of all children with pre-excitation have an additional heart disease.

Starting with Wolff, Parkinson and White's classic paper, this book gives a comprehensive summary of all important facts of pre-excitation, plus the authors' personal experiences of follow-up studies of patients through many decades. It also brings a broad view of the literature and discusses the different structural and physiological aspects which form the pathomechanism of pre-excitation.

The 13 Chapters Are a Co

1. General Considerati
2. The Electrocardiogr Syndrome: Complex
3. The Electrocardiogr Syndrome: Disturba
4. Pathology
5. Noninvasive Method
6. Invasive Methods of
7. Prognosis
8. Treatment
9. Problems of Diagno Cases
10. Summary of Findin excitation Syndrome
11. Concept of Interacti tional Factors
12. Explanation of Som excitation Syndrome
13. Various QRS Patter of Pre-excitation

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The Mary Gertrude Waters Professor of Cardiology and Chairman of the Department of Medicine, The University of Alabama in Birmingham, and Physician-in-Chief, University of Alabama Hospitals

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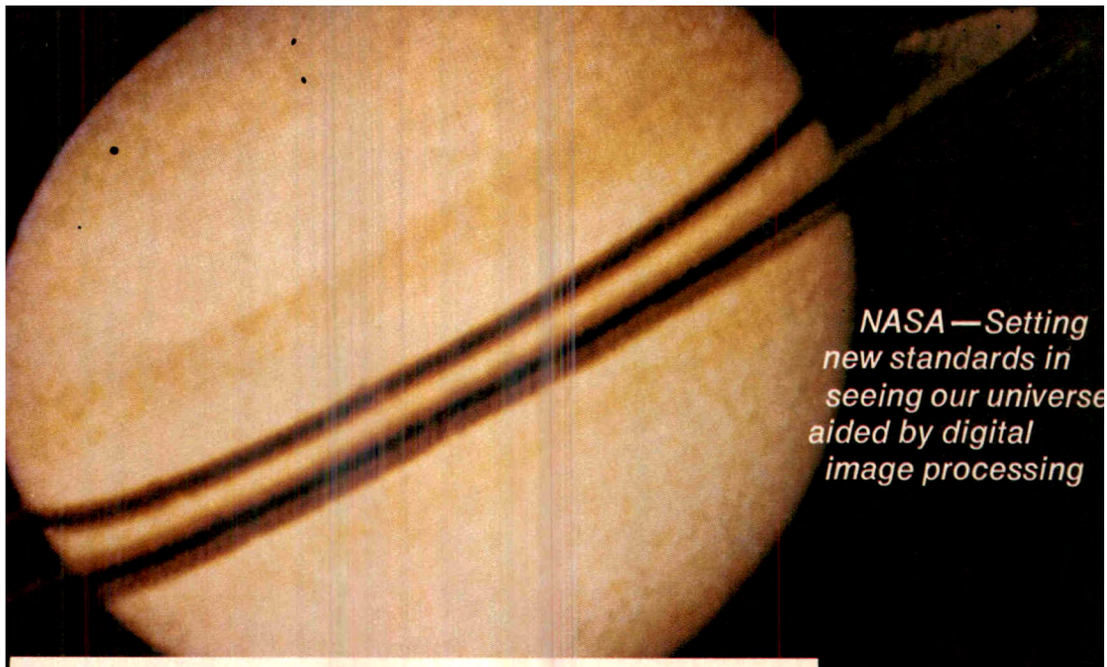

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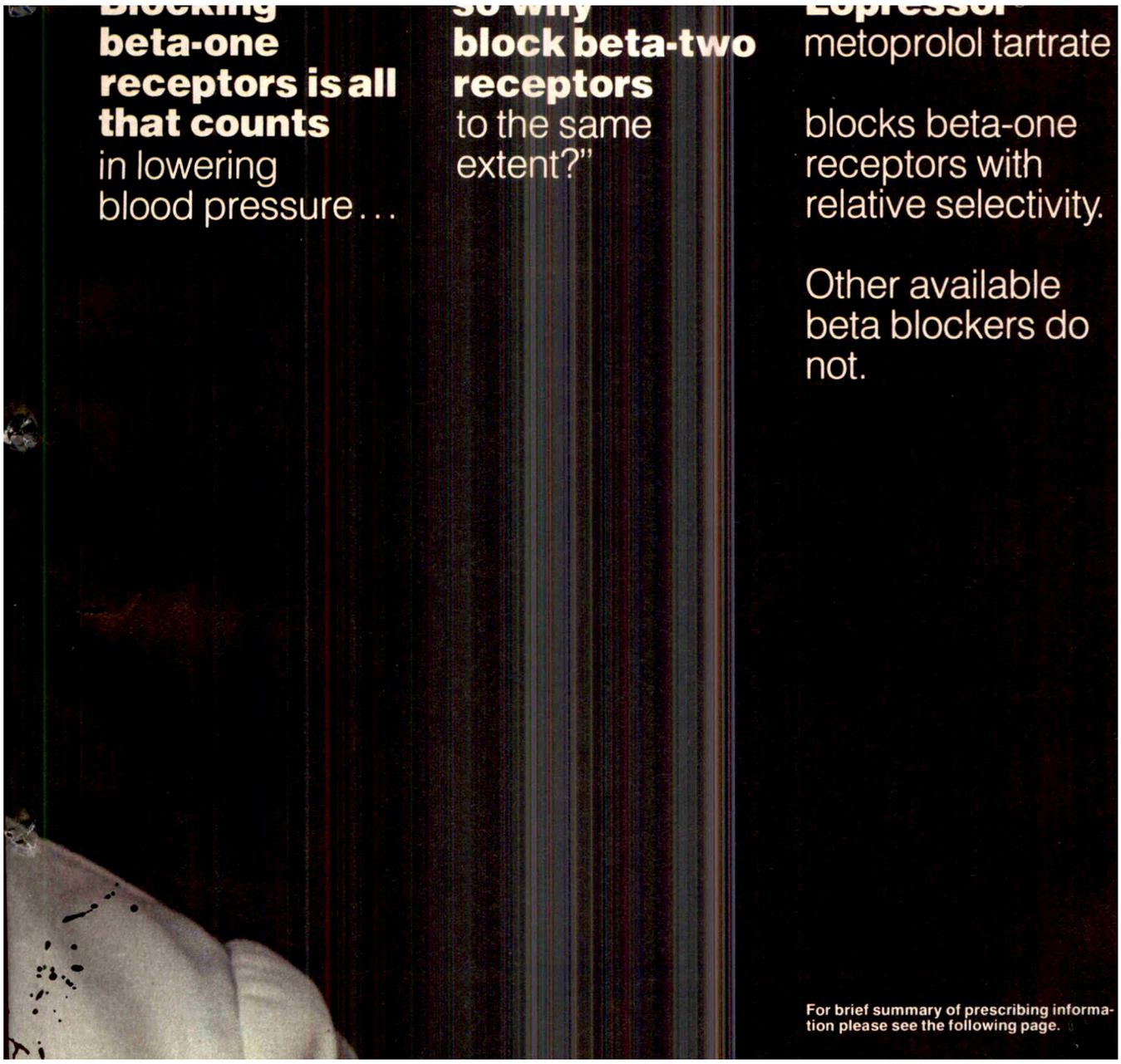
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Lopressor®
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An antihypertensive
beta-blocking agent

Brief Summary of Prescribing Information

Indications Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage in Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.

Allergic: Pruritus has occurred in less than 1 of 100 patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents, and should be considered potential adverse effects of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopressor should be individualized. The usual initial dose is 50 mg twice daily whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. Usual maintenance dosage is approximately 100 mg twice a day, with a range of 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower dosages are used, will experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose or three times daily therapy, may achieve better control. Beta$_1$ selectivity diminishes as dosage of Lopressor is increased.

This drug should be stored at controlled room temperature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

Store at controlled room temperature and protect from moisture.

Dispense in tight, light-resistant container (USP).

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For complete details, including description, clinical pharmacology and overdosage, please see full prescribing information.

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Pacing News

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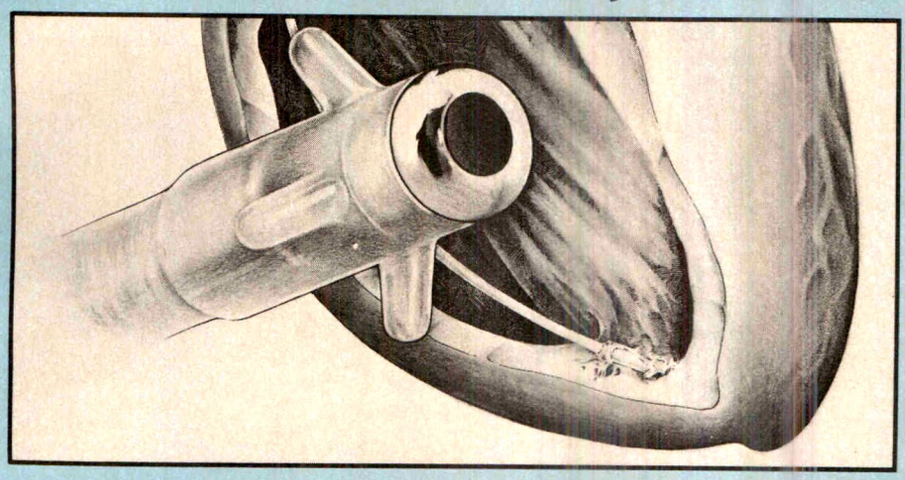

The ring-tipped electrode of the Model 6961-62 lead designed for enhanced electrical efficiency.

There are three reasons why Medtronic's Tenax™ tined leads have become the most prescribed endocardial leads in the world.

- Superior electrical performance offered by the ring-tip electrode design.
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- Greater theoretical lead longevity based on tests of the multifilar conductor coil.

Actually, three electrode design features contribute to this lead's superior performance.

For one thing, research has shown that its reduced electrode surface area (only 8 mm^2) is one of the best compromises between high current density for stimulation and an acceptable impedance affecting sensing. Of course, a reduced electrode surface area also minimizes pulse generator current drain.

Secondly, the gentle curvature of the tip electrode minimizes tissue trauma. This enhances performance by reducing the degree of myocardial tissue degeneration which often results in fibrotic build-up.

The configuration of the Model 6961-62 electrode concentrates the current field in the areas of curvature. This directs more available current into the endo/myocardium. Thus, overall electrode efficiency, primarily stimulation thresholds, is enhanced.

Besides outstanding electrical characteristics, lab tests of Medtronic's multifilar coil design show its having a potential flex life over 1,000 times greater than earlier endocardial lead designs which used a single-filament, nickel-alloy conductor.

Dislodgement is reduced by the small, soft, compliant tines on Medtronic's Tenax™ leads. They anchor within the cardiac structure of the ventricular chamber. In clinical studies, lead related reoperation incidence has averaged less than 5% for the Model 6961-62 leads, compared to 21% for a standard flanged endocardial lead without tines.

For a brochure showing the reoperation rates at nine medical centers, plus other information on Tenax™ 6961-62 leads, send in the coupon on the back.

Xyrel®–VP Pacemaker Meets Need of Sick Sinus Syndrome

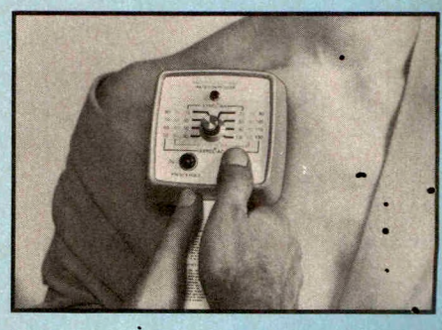
Flexibility–that's the benefit the rate programmable Xyrel®–VP pulse generator offers by allowing you to make periodic rate adjustments in your patients with progressive diseases such as sick sinus syndrome (SSS).

Here's how you can take advantage of the Xyrel®–VP rate programmability feature for your SSS patient: In the early stages of SSS, your patient may require pacing for just a few moments per month when the intrinsic rate drops below the rate determined for adequate cardiac output. The programmed rate allows a normal atrial-ventricular contraction sequence most of the time.

Since SSS is often a progressive disease, having the flexibility to change rate gives you the opportunity to treat a slowing of your patient's normal sinus rhythm. Frequently, this slowing is accompanied by a tendency toward a more unreliable rhythm. The SSS patient, therefore, becomes increasingly reliant on the pacemaker. As the disease progresses, you may elect to program the pacemaker to increasingly higher rates to maintain cardiac output when the pacemaker is needed to provide the dominant rhythm.

Also, an increase in pacemaker rate may be needed to prevent emergence of a less suitable tachyarrhythmia.

XYREL® continued on page 2



How the Xyrel®–VP Programmer is used to change pacemaker rate.

Medtronic Simplifies Pacemaker Follow-Up

Medtronic is making pacemaker follow-up easier and simpler than ever.

One way is with Cardiocare, a division of Medtronic which serves as a vital link between the physician and the pacemaker patient. At the physician's direction, Cardiocare provides a monitoring service which includes furnishing a transmitter, setting a fixed call schedule, review of EKG strips and pacemaker data by technicians and a cardiologist, regular reporting to the physician and 24-hour-a-day, seven-day-a-week emergency monitoring service.

Improved equipment is another. A modification has been made to Medtronic's standard Model 9401 Physician Receiver. Now it can receive and report pulse width reading from the newer Medtronic® transmitters in addition to rate and EKG tracing. Furthermore, existing 9401 units can be returned to Medtronic for modifications permitting pulse width readout.

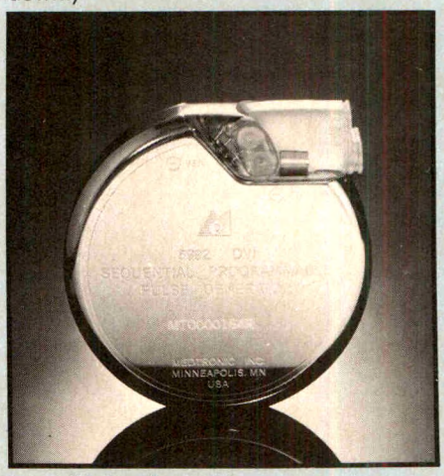
Patients will find the new Medtronic 9406 Patient Transmitter reliable and convenient. It can be applied to the patient's bare chest, or it can be used with fingertip electrodes as a table-top device. Although this small device weighs only 10 ounces, it transmits pulse rate and pulse width over most standard telephones.

NEW PRODUCTS ENHANCE UPPER CHAMBER PACING

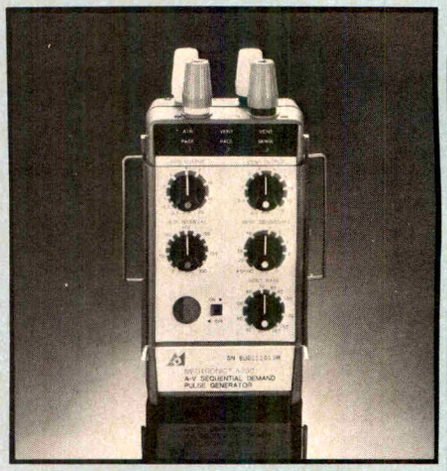
Both temporary and permanent A-V sequential pacing are likely to see more frequent applications because of two new products recently developed by Medtronic, Inc. These products are the Byrel™ implantable A-V sequential pacemaker and the Model 5330 external A-V sequential pacemaker. The new Byrel™ pacemaker, a programmable, lithium-powered, ventricular-inhibited device has seven A-V programs and one ventricular-inhibited mode (atrial portion of unit shutdown.)

The Byrel™ pacemaker has many of the performance features of other Medtronic pulse generators, including a lithium power source, titanium external covering, hermetically sealed hybrid electronics and more. Of course, both atrial and ventricular leads are required.

A companion to the Byrel™ is Medtronic's new 5330 external pacemaker designed for temporary atrial, ventricular or A-V sequential pacing.



Byrel™ implantable pacemaker designed for A-V sequential pacing.



Model 5330 external pacemaker for atrial, ventricular or A-V sequential pacing.

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- ☐ **Xyrel®–VP Pulse Generators**
- ☐ **Tenax™ Model 6961-62 Leads**
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5375 Sets Temporary Pacing Standards

For demand or asynchronous temporary ventricular pacing, Medtronic continues to be the pacemaker of choice in the CCU/ICU.

The 5375 is compact, yet offers the physician calibrated flexibility in controlling output, rate and sensitivity. It has many other features including push button lead connections and outstanding safety features. Send in the coupon for more information.

Model 5375 external pacemaker.

Xyrel® continued

Naturally, the Xyrel®–VP pacemaker offers the physician more than rate programming. Its programmed pulse width automatically compensates for the steady decrease in pacemaker voltage as the lithium cell depletes.

The rate you program is constant until it drops 5-11 beats per minute over a one-to-six-month period to signal that pulse generator replacement is indicated.

You can select from seven pacing rates (50, 60, 70, 75, 80, 90 and 100 ppm) and one diagnostic rate (30 ppm). It shares the outstanding proven reliability of all the Xyrel® series.

There's a Xyrel®–AP pacemaker, too, for atrial demand pacing.

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MEDTRONIC PRODUCT INFORMATION SUMMARY

Medtronic External Products

Intended Use—The Model 5330 and 5375 external pulse generators are intended for use with pacing lead systems for temporary cardiac pacing where such procedures are indicated for therapeutic, prophylactic or diagnostic purposes. The Model 5330 may be used for temporary atrial, ventricular or A-V sequential pacing. The 5375 is for ventricular pacing.

Contraindications—Atrial pacing should be used only in patients with intact A-V conduction systems. The existence of anomalous conduction pathways bypassing normal A-V conduction is a potential contraindication for atrial stimulation. In the A-V sequential pacing mode, use of the Model 5330 with certain implanted lead systems may be contraindicated. See the 5330 technical manual for more information.

Warnings—All electrical equipment that is used invasively or attached to a pacing lead system increases the patient's chances of exposure to potentially hazardous leakage currents. For complete information on the quality and degree of such exposure, consult the technical literature supplied with each product.

Precautions—All man-made devices are subject to malfunction. Appropriate standby equipment should be immediately available when temporary pacing is employed.

Potential Complications—Major potential complications related to temporary pacing are asystole following abrupt cessation of pacing and lead-system-related problems. Atrial stimulation carries, in addition, the potential complication of accidental high-rate ventricular stimulation possibly resulting in ventricular tachycardia or fibrillation.

Medtronic Monitoring and Follow-Up Devices

Intended Use—The TeleTrace® Telephone EKG System and the Model 9510 MiniClinic Pacemaker Monitor are intended for periodic, noninvasive monitoring of pacemaker function in the pacemaker patient.

There are no known contraindications, warnings or major potential complications associated with the use of this patient monitoring equipment. However, these devices should not be used or prescribed without prior study of the technical literature supplied with each product.

Medtronic® Implantable Pulse Generators

Intended Uses—Ventricular pacing using an implantable ventricular pulse generator and lead system are for long-term therapeutic control of heart rate in patients with impulse formation or conduction disorders leading to bradyarrhythmias, tachyarrhythmias and heart block (see product labeling for detailed list of intended uses). An atrial pulse generator is for long-term therapeutic control of heart rate in patients with impulse formation disorders but with intact, functioning A-V conduction systems. Cardiac pacing using an implantable A-V sequential pulse generator is for long-term therapeutic control of heart rate in patients where restoration of A-V synchrony is indicated to improve cardiac output or to protect against arrhythmias related to sequence of cardiac impulse propagation.

Contraindications—There are no known contraindications to the use of pacing as a therapeutic modality for the control of heart rate in patients with normal conduction systems. In certain patients with anomalies of the conduction system (WPW syndrome and related conditions), patients may be benefited or harmed by cardiac pacing. Therefore, electrophysiologic studies are required prior to therapeutic application of pacing. In addition, the patient's age and medical condition may dictate the particular pacing system and implantation procedure used by the physician.

Warnings—Diathermy should not be used on patients with pacemakers because of possible heat damage to electronic components. Electrosurgical units should never be used in the vicinity of unipolar pulse generators or bipolar pulse generators implanted in the unipolar mode because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead. Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator.

Precautions—The physician should be aware that all pulse generators will ultimately cease to function due to cell depletion and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also, that the pacing system may cease to function at any time due to lead-related problems such as displacement, fracture, fibrotic tissue formation, elevated thresholds and medical complications, and that proper operation may be affected by electrical interference from certain electrical equipment.

Side Effects—Body rejection phenomena, including local tissue reaction, muscle and nerve stimulation, infection, erosion of pulse generator/lead through skin, transvenous lead-related thrombosis, embolism and cardiac tamponade.

Medtronic® Implantable Pacing Leads and Accessories

Intended Use—Medtronic® Implantable pacing leads are designed to be used with Medtronic® pulse generators as part of a cardiac pacing system (see product labeling for specific directions regarding applications).

Contraindications—Endocardial pacing leads are contraindicated in the presence of tricuspid valvular disease.

Warnings—An implanted lead or lead/adaptor combination constitutes a direct, low resistance current path to the myocardium. During the connection and testing procedures, only battery-powered pulse generators should be used with the lead system to protect against ventricular fibrillation induced by alternating current leakage. Extreme caution must be taken to properly ground all line-powered equipment used in the vicinity of the patient. Lead adaptors, lead extenders and repair kits should not be used if the integrity of the lead is in doubt.

Precautions—The pacing system may cease to function due to lead-related problems such as displacement, fracture, fibrotic tissue formation and elevated thresholds.

Side Effects—Body rejection phenomena, infection, erosion or migration through body tissue, transvenous lead-related thrombosis embolism.

How Supplied—Medtronic® permanent implantable leads and accessories are supplied sterilized and, in most cases, individually packaged.

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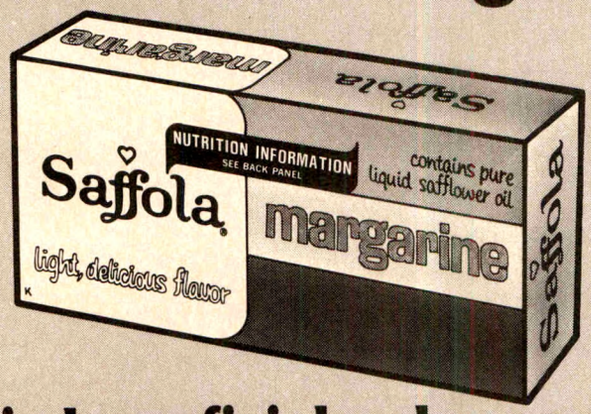

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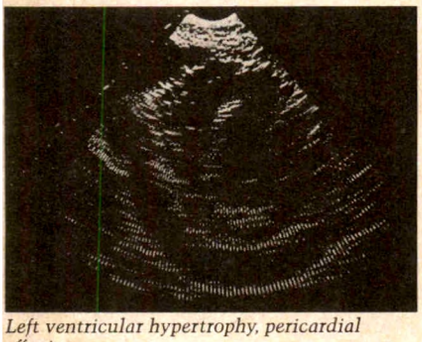
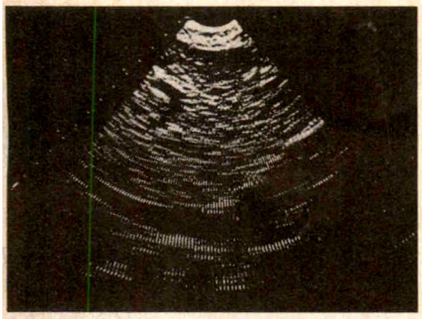


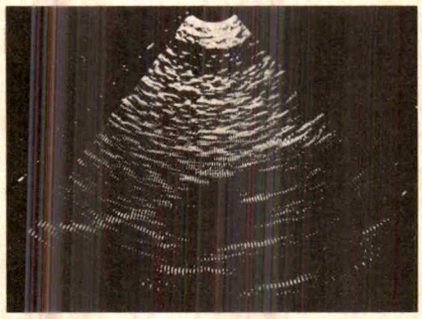
Left ventricular hypertrophy, pericardial effusion.

Normal

Pericardial effusion.

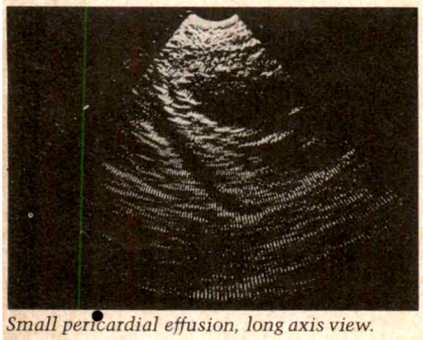


Inferior Vena Cava entering right atrium.

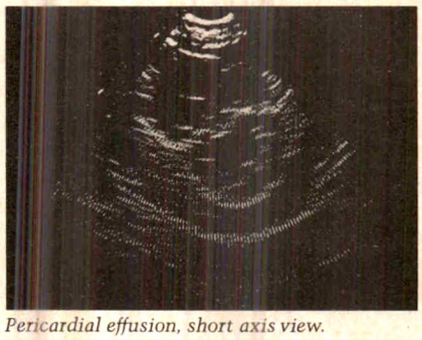


Normal

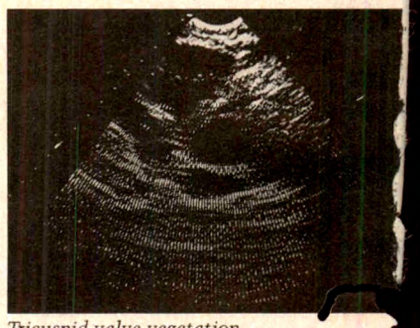
Tricuspid valve vegetation.



Small pericardial effusion, long axis view.



Pericardial effusion, short axis view.



Tricuspid valve vegetation.

Our patented method of Dynamic Image Reconstruction significantly improves image quality, data storage and the ease of making a diagnosis.

This unique system delivers dimensionally correct, high-resolution wide angle images with none of the distortion produced by conventional methods.

As a result, you can more accurately visualize cross-sections of the entire adult heart—parasternal short and long axis views as well as apical, subxyphoid and others. You can also use it for A-mode and M-mode examinations.

What's more, Dynamic Image Reconstruction lets you preserve both two-dimensional images and M-mode on video cassettes. On playback, you can get a hard copy of both, you can reformat the image and you can reconstruct M-mode tracings from recorded two dimensional images.

Ultrasound is changing fast. With EkoSector I, you'll be ready.

Thanks to our exclusive system of Dynamic Image Reconstruction, the data acquisition and display capability of EkoSector I is virtually obsolescence-free.

Images recorded with the Dynamic Image Reconstruction

Defibrillators for the ospital have always been a ompromise.

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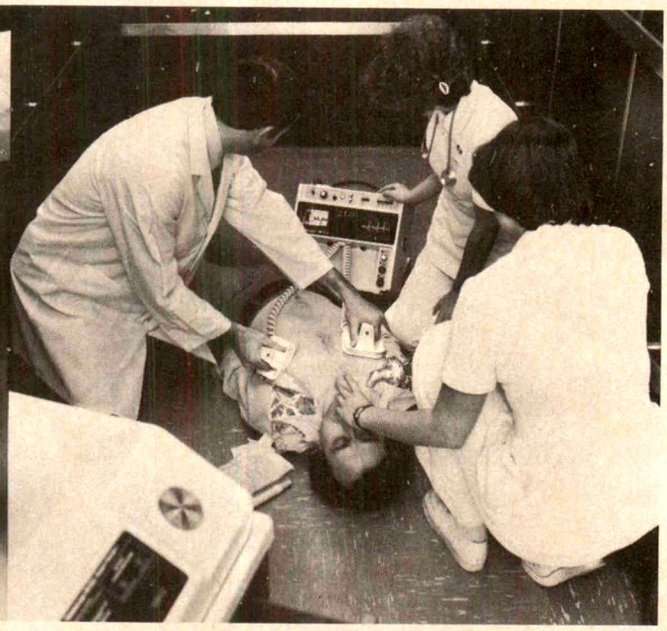

We're pleased to offer you first defibrillator system t doesn't force you to com- omise: the Datascope Hospital stem.

The Datascope Hospital stem is the M/D3 defibrillator/ ton recorder and the support dule in which it nests.

Since you may need a ibrillator on a cart, or a rtable to reach and transport a tient, we designed the M/D3 like other defibrillators.

The Datascope Hospital stem separates in a manner that kes sense. The defibrillator, nitor and recorder all remain ct as a compact unit. So you ays have everything you need with you where you need it, when you need it. The support module separates and remains on the crash cart, leaving unnecessary weight behind.

On or off a crash cart, it has features found in no other system.

The scope on the Hospital System is 5″ in diameter. The same size as scopes on defibrillators weighing 35 to 40 pounds.

The monitor offers 2 large digital displays. One for heart rate and one for delivered energy. (To our mind, lights are simply not an adequate indication of such critical parameters.)

The support module for the Datascope Hospital System has a built-in delivered energy tester. Here again, instead of a light that merely indicates, there's a meter that accurately measur the delivered energy throughout the entire range of the defibrillator.

There's a document switch on the defibrillator paddles to trigger the strip chart recorder. And the paddles rapidly disconnect for easy changes or replacement.

Perhaps the most importa innovation of all, ours is the fi defibrillator system to end the fear of battery failure.

The M/D3 incorporates three totally independent power systems: comple ac line operation, nickel-cadmium batteri that recharge in less tha five hours, and the wor first Lithium Emergenc Power Pack. This revolutionary power pack remains fully-charged in the unit for up to 5 years. In the event that all other pow sources fail, you merely activate the Emergency Pack to instantly power the monitor and defibrillator.

For all of its features, the M/D3 weighs less than 28 pounds and is extremely easy to operate.

We urge you to see a demonstration of the new Datascope Hospital System. There has never been any defibrillator in a hospital like it On or off a crash cart.

To arrange for a demonstra tion call us at 201-265-8800. Datascope Corp., Box 5-AA, Paramus, NJ 07652. In Europe: Datascope B.V., Post Box 26, 3870 CA, Hoevelaken, Holland

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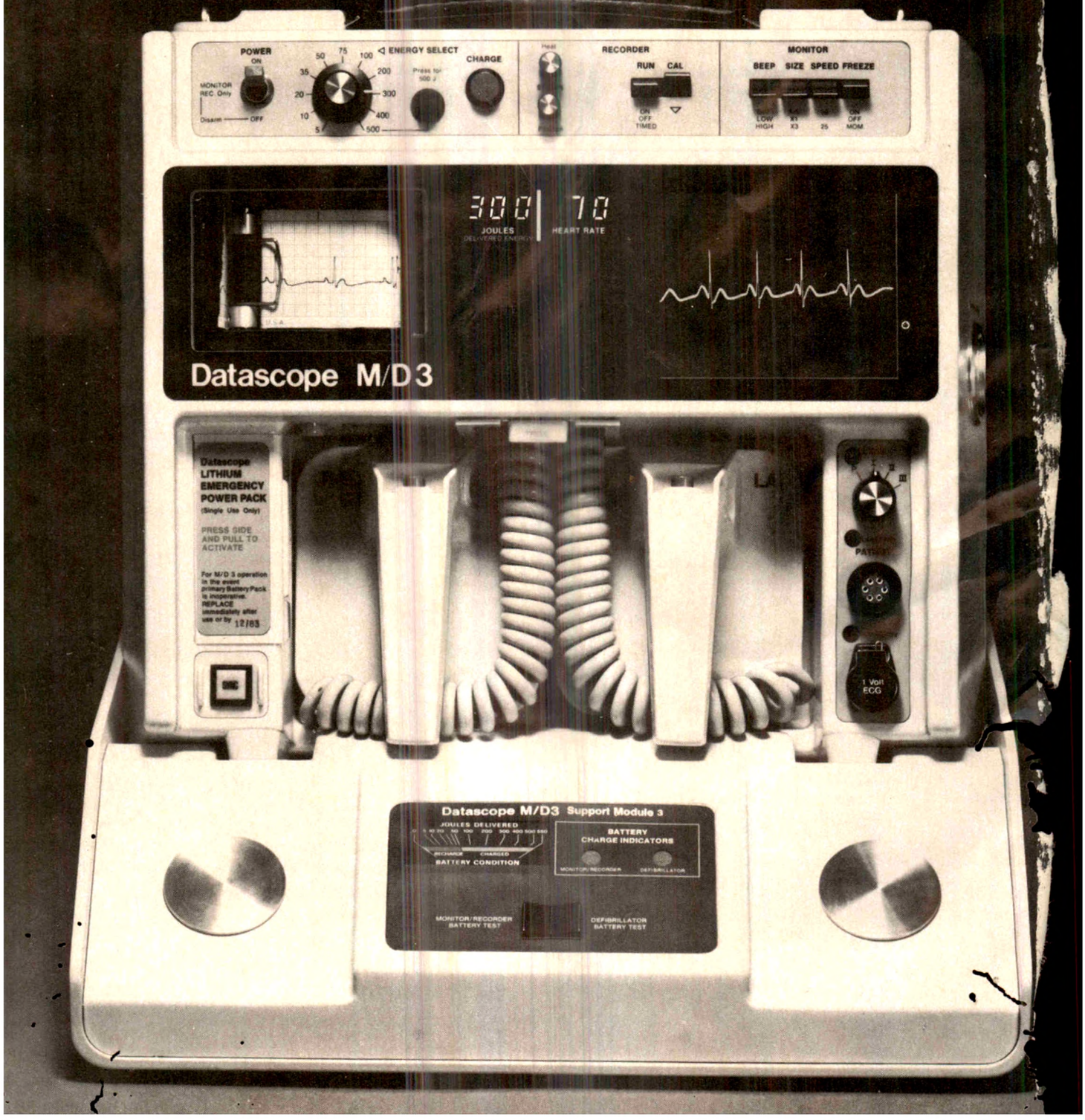

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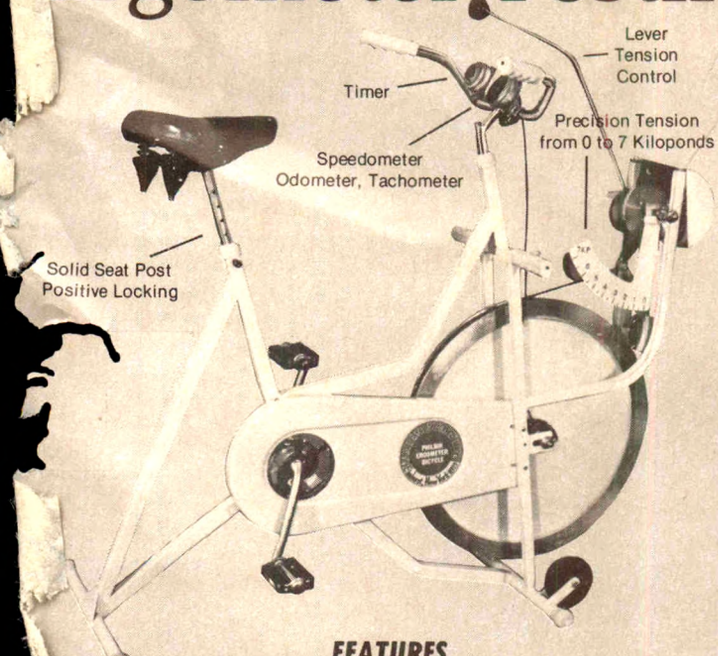

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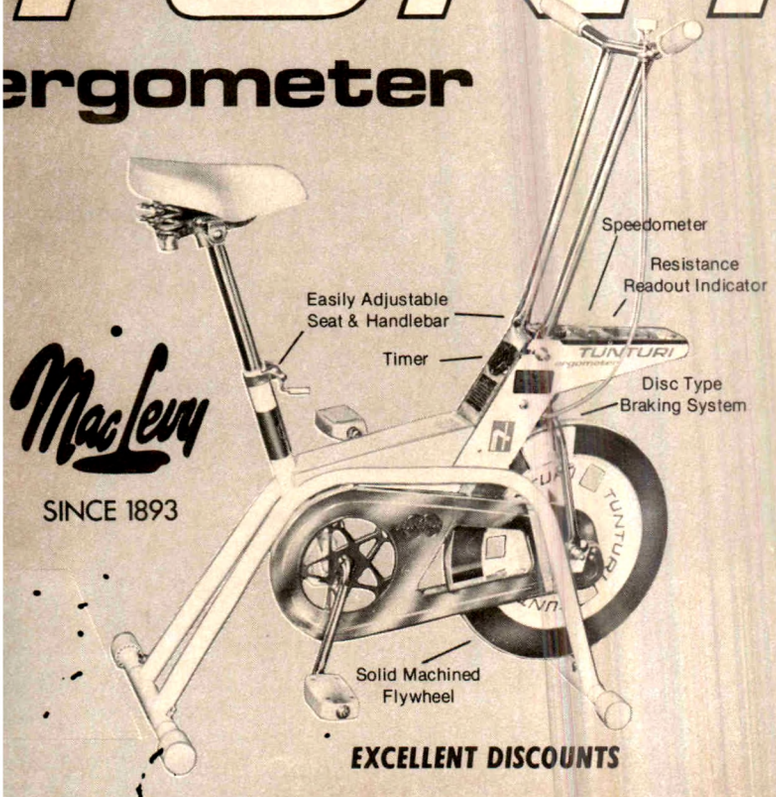

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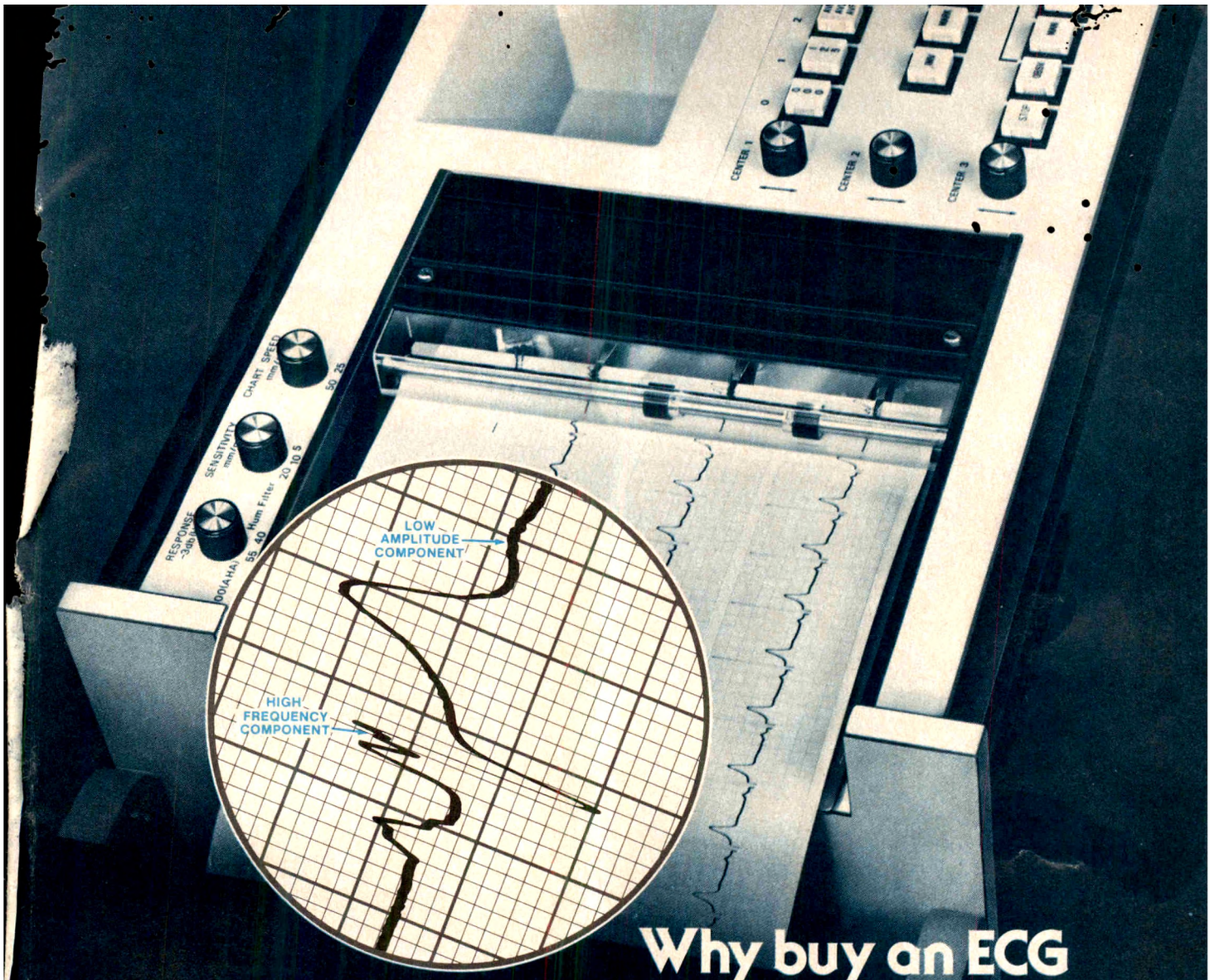

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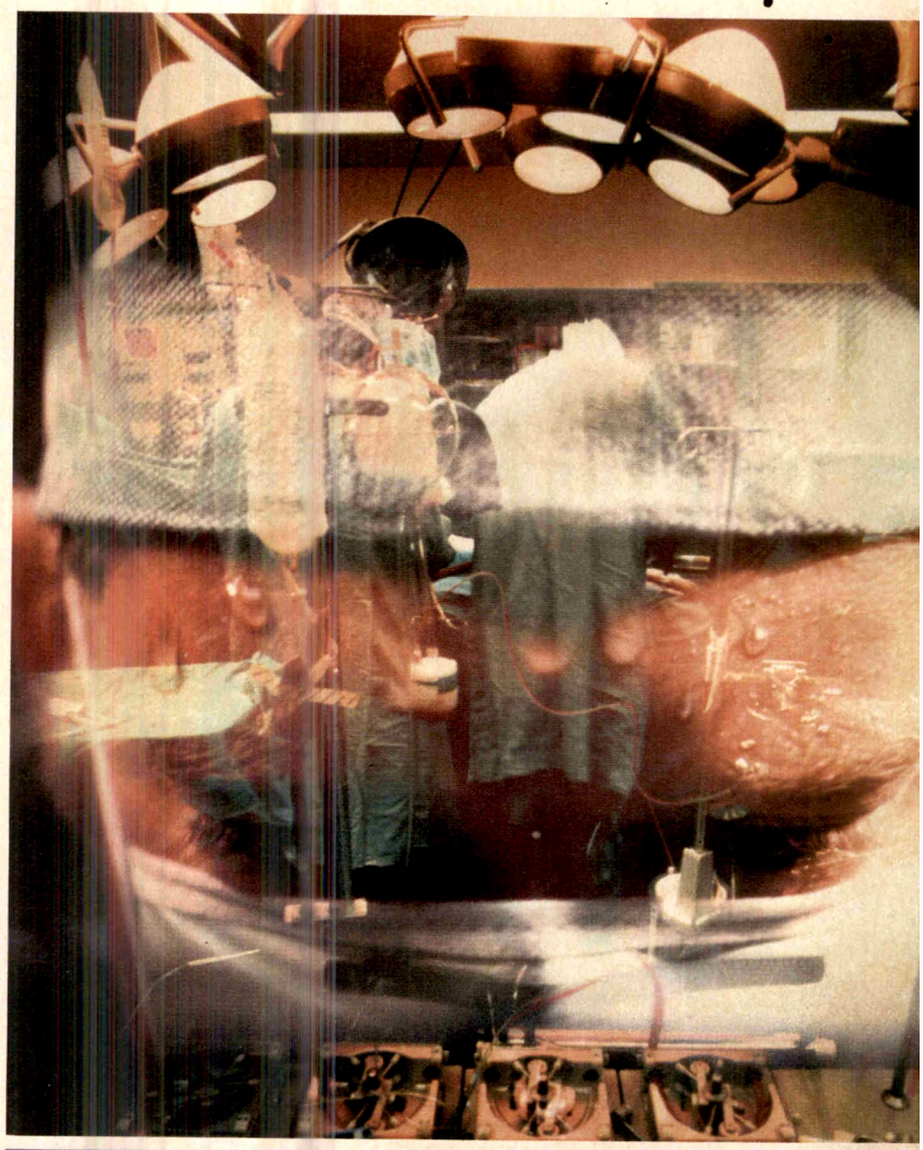

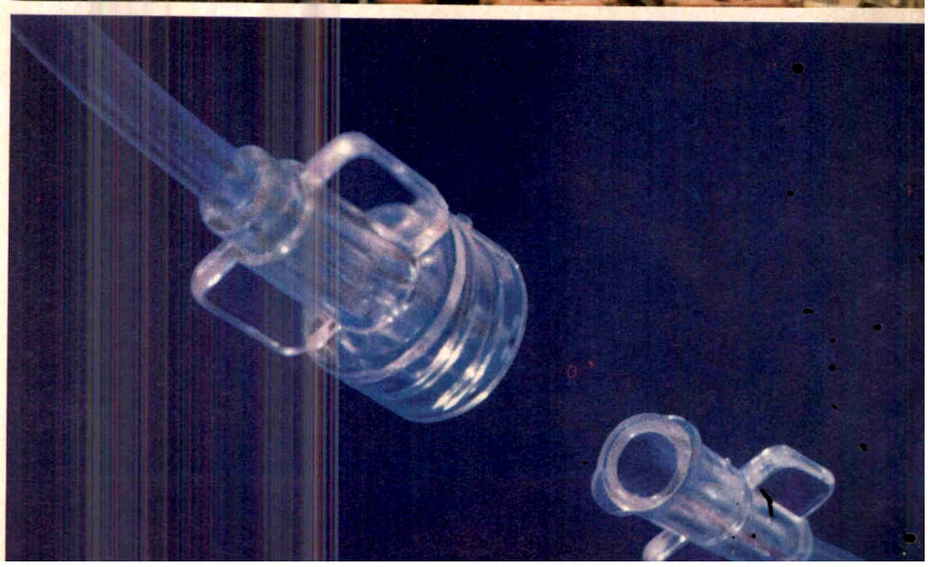

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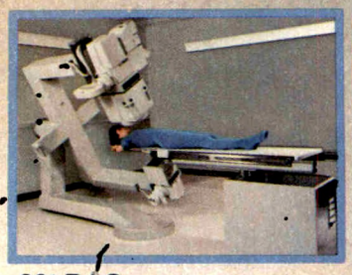
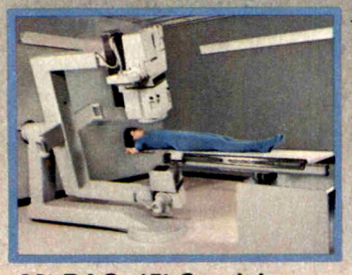
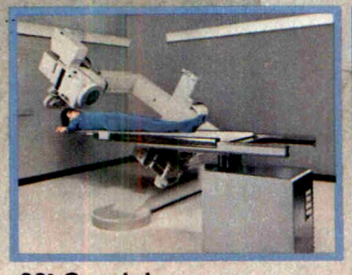


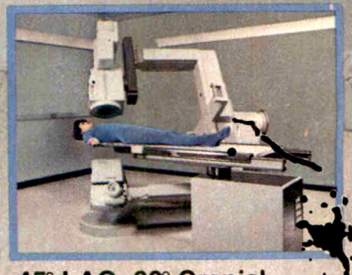
30° RAO



20° RAO, 15° Caudal



60° Cranial



45° LAO, 30° Cranial

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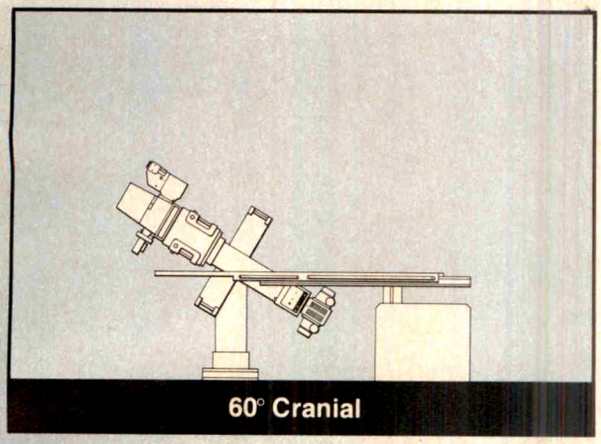
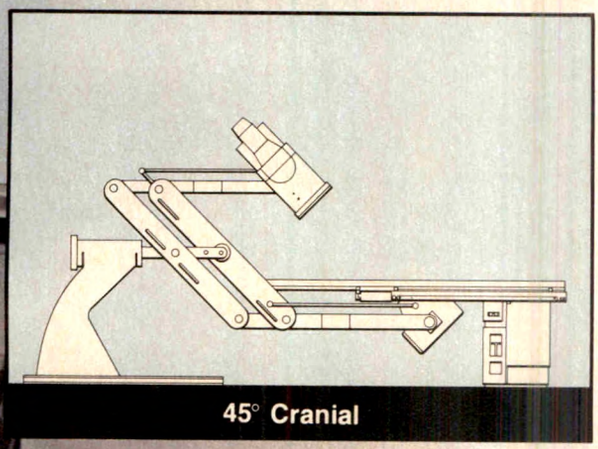


60° Cranial

Space-saving design of the new GE system (above) is compared to a conventional unit (below).



45° Cranial

GE's new L/U system gives you compact design and motorized positioning.

Here's a new vascular system that provides the full range of imaging positions for cardiac, neuro, abdominal and peripheral angiography without patient rotation or movement. It requires one-third less floor space than a conventional system... and costs less too.

It's the new L/U system from General Electric.

Either motorized or manual positioning can be used to rapidly obtain AP, PA, lateral, oblique or compound views.

The unique stand allows universal positioning of the tube and intensifier anywhere in the transverse, vertical and longitudinal axes. The table provides triaxial movement plus rotary positioning to cover the entire anatomical range. And the low absorption carbon fiber reinforced top facilitates high contrast studies.

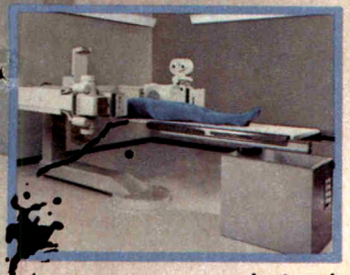
You'll also get the proven performance of the Fluoricon® 300 intensifier. With 9″ triple field capability. And superior 14.5 megahertz bandwidth video imaging with high mA cine and photospot recording. Resolution, contrast ratios and quantum detection efficiency are optimized for vascular procedures.

Ask your GE representative about the new L/U system. It gives you all the angles and all the room you'll ever need.

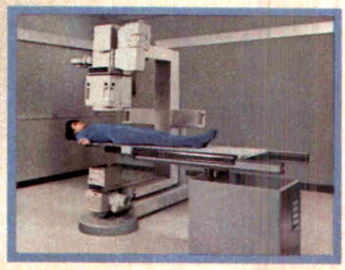
General Electric Medical Systems,
Milwaukee, Toronto, Madrid.

You'd expect it from GE.

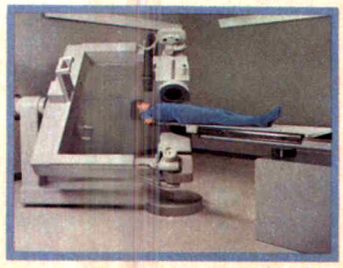
GENERAL ELECTRIC



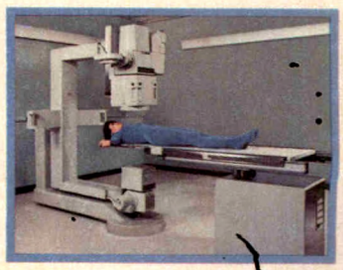
Lateral



PA



45° LAO, 40° Cranial



PA

WHEN YOU SUSPECT OR DETECT VENOUS THROMBOSIS...

Thromboembolism: a high risk among patients with one or more of these factors...

Advanced age
Fractures of lower limb
Hip surgery
Pelvic or abdominal surgery with extensive dissection
Previous venous thromboembolism
Congestive cardiac failure
Cancer surgery
Obesity
Varicose vein surgery

Incidence of venous thrombosis or abnormal scans as shown by ^{125}I-fibrinogen screening in selected high-risk medical-surgical patients

Category	Incidence
Elective surgery	
Major abdominal thoracic/gynecologic	11-65%[1,2]
Retropubic prostatectomy	28-50%[1,2]
Transurethral prostatectomy	4%[1,2]
Emergency surgery	
Hip fracture	48-74%[1,2]
Childbirth	3%[1,2]
Medical	
Myocardial infarction	23-38%[1,2]
Stroke	60%[1]

ORAL ANTICOAGULATION:
Often indicated to lower the risk of thromboembolic complications.

References: 1. Hirsh J, Gallus AS: ^{125}I-labeled fibrinogen scanning. Use in the diagnosis of venous thrombosis. *JAMA 233*:970-973, 1975. **2.** Kakkar VV: The diagnosis of deep vein thrombosis using the ^{125}I-fibrinogen test. *Arch Surg 104*:152-159, 1972. **3.** Ebert RV: Use of anticoagulants in acute myocardial infarction. *Circulation 45*:903-910, Apr 1972. **4.** Borden CW: The current status of therapy with anticoagulants. *Med Clin North Am 56*:235-251, Jan 1972. **5.** Hirsh J, Gallus AS: Anticoagulants in venous thromboembolism. Prophylactic and therapeutic use. *Postgrad Med 55*:211-217, Jan 1974.

*For selected patients who have had a large infarct, a history of previous infarction or angina, severe hypotension or shock, chronic atrial fibrillation, congestive heart failure, past history of venous thrombosis or embolism or complications requiring a prolonged period in bed.

Endo Laboratories DUPONT

COUMADIN is an Endo registered U.S. trademark.

The oral anticoagulant of choice:

Tablets
COUMADIN®
crystalline warfarin sodium

singled out by more than 20 years of experience

Effective prophylaxis and treatment of venous thrombosis
Effective prophylaxis and treatment of pulmonary embolism
Effective treatment of atrial fibrillation with embolization
Effective adjunctive treatment of coronary occlusion

Initiation of therapy

Induction—40 to 60 mg for average adult or 20 to 30 mg for elderly and/or debilitated patients for one dose only administered orally, intravenously or intramuscularly.

Alternatively, the large priming dose may be decreased for all patients to minimize the possibility of excessive increases in prothrombin time. Induction may be initiated with 10 to 15 mg daily and thereafter (usually 2 or 3 days) adjusted according to prothrombin time response.

- dosage must be individualized according to patient's prothrombin time
- frequent laboratory monitoring is recommended
- determine prothrombin time daily until results fall within the therapeutic range—1.5 to 2.5 times normal
- afterwards, prothrombin time must be determined periodically to monitor the patient's course

Maintenance of anticoagulation

- 2-10 mg, for most patients (scored tablets allow flexibility and accurate titration)
- dose and interval should be adjusted according to the individual patient's prothrombin time response

Duration of anticoagulation

- should be individualized for each patient
- in general, should be continued until danger of thrombosis and embolism has passed

Recommendations of prominent clinicians on duration of therapy

in myocardial infarction[3,4*]	1-3 years* (reevaluate at least every 6 months)
in pulmonary embolism[4,5]	6 weeks-6 months
in deep vein thrombosis[4,5]	6 weeks-6 months

Before prescribing, please see full product information on next page.

COUMADIN® Tablets
for long- and short-term oral anticoagulation...
crystalline warfarin sodium, U.S.P.*

DESCRIPTION COUMADIN (crystalline warfarin sodium), a prothrombinopenic anticoagulant, is chemically crystalline sodium warfarin isopropanol clathrate. The crystallization of warfarin sodium virtually eliminates trace impurities present in amorphous warfarin sodium, thus achieving a crystalline product of the highest purity. Warfarin* is the coined generic name for 3-(α-Acetonylbenzyl)-4-hydroxycoumarin. On a dose-for-dose basis, COUMADIN (crystalline warfarin sodium) is therapeutically equivalent to amorphous warfarin sodium.

ACTIONS COUMADIN and other coumarin anticoagulants act by depressing synthesis in the liver of several factors which are known to be active in the coagulation mechanisms in a variety of diseases characterized by thromboembolic phenomena. The resultant **in vivo** effect is a sequential depression of Factors VII, IX, X and II. The degree of depression is dependent upon the dosage administered. Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischemic tissue damage. However, once a thrombosis has occurred, anticoagulant treatment aims to prevent further extension of the formed clot and prevents secondary thromboembolic complications which may result in serious and possible fatal sequelae.

After oral administration, absorption is essentially complete, and maximal plasma concentrations are reached in 1 to 9 hours. Approximately 97% is bound to albumin within the plasma. COUMADIN usually induces hypoprothrombinemia in 36 to 72 hours, and its duration of action may persist for 4 to 5 days, thus producing a smooth, long lasting response curve. Little is known of the metabolic pathways involved in the biotransformation of oral anticoagulants in man. However their metabolites appear to be eliminated principally in the urine.

INDICATIONS Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

Effective: COUMADIN is indicated for the prophylaxis and treatment of venous thrombosis and its extension, the treatment of atrial fibrillation with embolization, the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion.

"Possibly" effective: as an adjunct in the treatment of transient cerebral ischemic attacks.

Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATIONS Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than its potential clinical benefits, such as:

Pregnancy—COUMADIN is contraindicated in pregnancy because the drug passes through the placental barrier and may cause fatal hemorrhage to the fetus in utero. Furthermore, there have been reports of birth malformations in children born to mothers who have been treated with warfarin during pregnancy. Women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed with the patient. If the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks.

Hemorrhagic tendencies or blood dyscrasias. Recent or contemplated surgery of: (1)central nervous system; (2)eye; (3)traumatic surgery resulting in large open surfaces. **Bleeding tendencies associated with active ulceration or overt bleeding of:** (1)gastrointestinal, genitourinary or respiratory tracts; (2)cerebrovascular hemorrhage; (3)aneurysms—cerebral, dissecting aorta; (4)pericarditis and pericardial effusions; (5)subacute bacterial endocarditis. **Threatened abortion,** eclampsia and preeclampsia. **Inadequate laboratory facilities** or unsupervised senility, alcoholism, psychosis; or lack of patient cooperation. **Spinal puncture** and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding. **Miscellaneous:** major regional, lumbar block anesthesia and malignant hypertension.

WARNINGS Warfarin sodium is a potent drug with a half-life of 2½ days; therefore its effects may become more pronounced as daily maintenance doses overlap. It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. Dosage should be controlled by periodic determinations of prothrombin time or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage prothrombin time. Therefore, to obtain a valid prothrombin time when heparin and COUMADIN are given together, a period of at least 5 hours should elapse after the last intravenous dose and 24 hours after the last subcutaneous dose of heparin, before blood is drawn.

Caution should be observed when warfarin sodium is administered in any situation or physical condition where added risk of hemorrhage is present.

Administration of anticoagulants in the following conditions will be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the risk of thrombosis or embolization in untreated cases. The following may be associated with these increased risks:

Lactation—coumarins may pass into the milk of mothers and cause a prothrombinopenic state in the nursing infant. **Severe to moderate hepatic or renal insufficiency. Infectious diseases or disturbances of intestinal flora**—sprue, antibiotic therapy. **Trauma** which may result in internal bleeding. **Surgery or trauma** resulting in large exposed raw surfaces. **Indwelling catheters. Severe to moderate hypertension. Miscellaneous:** polycythemia vera, vasculitis, severe diabetes, severe allergic and anaphylactic disorders.

Patients with congestive heart failure may become more sensitive to COUMADIN, thereby requiring more frequent laboratory monitoring, and reduced doses of COUMADIN.

Concurrent use of anticoagulants with streptokinase or urokinase is not recommended and may be hazardous. (Please note recommendations accompanying these preparations.)

Abrupt cessation of anticoagulant therapy is not generally recommended; taper dose gradually over three to four weeks.

PRECAUTIONS Periodic determination of prothrombin time or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional prothrombin time determinations in the period immediately after discharge from the hospital, and whenever other medications are initiated, discontinued or taken haphazardly. The following factors are listed for your reference; however, other factors may also affect the prothrombin response.

The following factors, alone or in combination, may be responsible for increased prothrombin time response:

ENDOGENOUS FACTORS: Carcinoma; collagen disease; congestive heart failure; diarrhea; elevated temperature; hepatic disorders—infectious hepatitis, jaundice; poor nutritional state; vitamin K deficiency—steatorrhea.

EXOGENOUS FACTORS: Alcohol†; allopurinol; aminosalicylic acid; anabolic steroids; antibiotics; bromelains; chloral hydrate†; chlorpropamide; chymotrypsin; cimetidine; cinchophen; clofibrate; COUMADIN (crystalline warfarin sodium) overdosage; dextran; dextrothyroxine; diazoxide; dietary deficiencies; diuretics†; disulfiram; drugs affecting blood elements; ethacrynic acid; glucagon; hepatotoxic drugs; indomethacin; inhalation anesthetics; mefenamic acid; methyldopa; methylphenidate; metronidazole; monoamine oxidase inhibitors; nalidixic acid; oxolinic acid; oxyphenbutazone; phenylbutazone; phenyramidol; prolonged hot weather; prolonged narcotics; quinidine; quinine; salicylates; sulfinpyrazone; sulfonamides, long acting; thyroid drugs; tolbutamide; triclofos sodium; trimethoprim/sulfamethoxazole; unreliable prothrombin time determinations.

The following factors, alone or in combination, may be responsible for decreased prothrombin time response:

ENDOGENOUS FACTORS: Diabetes mellitus; edema; hereditary resistance to coumarin therapy; hyperlipemia; hypothyroidism.

EXOGENOUS FACTORS: Adrenocortical steroids; alcohol†; antacids; antihistamines; barbiturates; chloral hydrate†; chlordiazepoxide; cholestyramine; COUMADIN underdosage; diet high in vitamin K (vegetables, fish, fish oil, onions); diuretics†; ethchlorvynol; glutethimide; griseofulvin; haloperidol; meprobamate; oral contraceptives; paraldehyde; primidone; rifampin; unreliable prothrombin time determinations; vitamin C.

†Increased and decreased prothrombin time responses have been reported.

*Present as crystalline sodium warfarin isopropanol clathrate.

A patient may be exposed to a combination of the above factors, some of which may increase and some decrease his sensitivity to COUMADIN. Because the net effect on his prothrombin time response may be unpredictable under these circumstances, more frequent laboratory monitoring is advisable.

Drugs not yet shown to interact or not to interact with coumarins are best regarded with suspicion, and when their administration is started or stopped, the prothrombin time should be determined more often than usual.

Coumarins also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (diphenylhydantoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

ADVERSE REACTIONS Potential side effects of COUMADIN (crystalline warfarin sodium) include:

1. Minor or major hemorrhage from any tissue or organ—which is an extension of the physiologic activity of prothrombinopenia. The signs and symptoms will vary according to the location and degree or extent of the bleeding. Therefore the possibility of hemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with prothrombin activity. (See TREATMENT FOR OVERDOSAGE.)

Bleeding which occurs when the prothrombin time is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g. tumor, ulcer, etc.

2. Side effects other than hemorrhage are infrequent and consist of alopecia, urticaria, dermatitis, fever, nausea, diarrhea, abdominal cramping, a syndrome called "purple toes," hypersensitivity reactions and a reaction consisting of hemorrhagic infarction and necrosis of the skin.

3. Priapism has been associated with anticoagulant administration, however, a causal relationship has not been established.

DOSAGE AND LABORATORY CONTROL The aim of anticoagulant therapy is to impede the coagulation or clotting mechanism to such an extent that thrombosis will not occur, but at the same time avoiding such extensive impairment as might produce spontaneous bleeding. Effective therapeutic levels with minimal complications can best be achieved in cooperative and well-instructed patients, who keep the doctor informed of their status between visits. COUMADIN patient aids are available to physicians on request.

The administration and dosage of COUMADIN must be individualized for each patient according to the particular patient's sensitivity to the drug as indicated by the prothrombin time. The prothrombin time reflects the depression of vitamin K dependent Factors VII, X and II. These factors, in addition to Factor IX, are affected by coumarin anticoagulants. There are several modifications of the Quick one-stage prothrombin time and the physician should become familiar with the specific method used in his laboratory.

Administration of COUMADIN should be gauged according to prothrombin time determinations by a suitable method. The blood prothrombin time should usually be determined daily after the administration of the initial dose until prothrombin time results stabilize in the therapeutic range. Intervals between subsequent prothrombin time determinations should be based upon the physician's judgment of the patient's reliability and response to warfarin in order to maintain the individual within the therapeutic range. Acceptable intervals for prothrombin time determinations have usually fallen within the range of one to four weeks. Satisfactory levels for maintenance of therapeutic anticoagulation are 1½ to 2½ times the normal prothrombin time (e.g. 18 to 30 seconds, with a control of 12 seconds).

Induction—40 to 60 mg for average adult or 20 to 30 mg for elderly and/or debilitated patients for one dose only administered orally, intravenously or intramuscularly.

Alternatively, the large priming dose may be decreased for all patients to minimize the possibility of excessive increases in prothrombin time. Induction may be initiated with 10 to 15 mg daily and thereafter (usually 2 or 3 days) adjusted according to prothrombin time response. The basis for the no-loading dose regimen is that the depression of Factors II, IX, and X are not accelerated by the administration of a loading dose.

Maintenance—Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response.

Duration of therapy—The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Treatment during dentistry and surgery—The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. Interruption of anticoagulant therapy may precipitate thromboembolism, and conversely, if anticoagulants are maintained at full doses, some patients may hemorrhage excessively. If it is elected to administer anticoagulants prior to, during, or immediately following dental or surgical procedures, it is recommended that the dosage of COUMADIN (crystalline warfarin sodium) be adjusted to maintain the prothrombin time at approximately 1½ to 2½ times the control level. The operative site should be sufficiently limited to permit the effective use of local procedures for hemostasis including absorbable hemostatic agents, sutures, and pressure dressings if necessary. Under these conditions dental and surgical procedures may be performed without undue risk of hemorrhage.

COUMADIN with Heparin—Since a delay intervenes between the administration of the initial dose and the therapeutic prolongation of prothrombin time, it may be advisable in emergency situations to administer sodium heparin initially along with COUMADIN. The initial dose of heparin and injectable COUMADIN may be administered together in the same syringe. It should be noted that heparin may affect the prothrombin time, and therefore, when patients are receiving both heparin and COUMADIN, the blood sample for prothrombin time determination should be drawn just prior to the next heparin dosage, at least 5 hours after the last intravenous injection or 24 hours after the last subcutaneous injection.

TREATMENT FOR OVERDOSAGE Excessive prothrombinopenia, with or without bleeding, is readily controlled by discontinuing COUMADIN (crystalline warfarin sodium), and if necessary, the oral or parenteral administration of vitamin K_1. The appearance of microscopic hematuria, excessive menstrual bleeding, melena, petechiae or oozing from nicks made while shaving are early manifestations of hypoprothrombinemia beyond a safe and satisfactory level.

In excessive prothrombinopenia with mild or no bleeding, omission of one or more doses of COUMADIN may suffice; and if necessary, small doses of vitamin K_1 orally, 2.5 to 10 mg, will usually correct the problem.

If minor bleeding persists, or progresses to frank bleeding, vitamin K_1 in doses of 5 to 25 mg may be given parenterally. (Please note recommendations accompanying vitamin K preparations prior to use.)

Fresh whole blood transfusions should be considered in cases of severe bleeding or prothrombinopenic states unresponsive to vitamin K_1.

Resumption of COUMADIN administration reverses the effect of vitamin K_1, and a therapeutic hypoprothrombinemia level can again be obtained.

SUPPLIED Tablets: COUMADIN (crystalline warfarin sodium). For oral use, single scored, imprinted numerically with potency as follows: 2 mg lavender, 2½ mg orange, 5 mg peach, 7½ mg yellow, 10 mg white. In bottles of 100 and 1000. Also available in Hospital Unit-Dose blister package of 100.

Injection: Available as single injection units of amorphous warfarin sodium lyophilized for intravenous or intramuscular use in a box of 6 units for use immediately after reconstitution.

50 mg: Unit consists of 1 vial, 50 mg; sodium chloride, 10 mg; thimerosal, 0.2 mg. pH is adjusted with sodium hydroxide; accompanied by a 2 ml ampul Sterile Water for Injection.

Sterile Water for Injection contains no antimicrobial or other substance, and it is not suitable for intravascular injection without first having been made approximately isotonic by the addition of a suitable solute. Use only for reconstitution of the lyophilized product.

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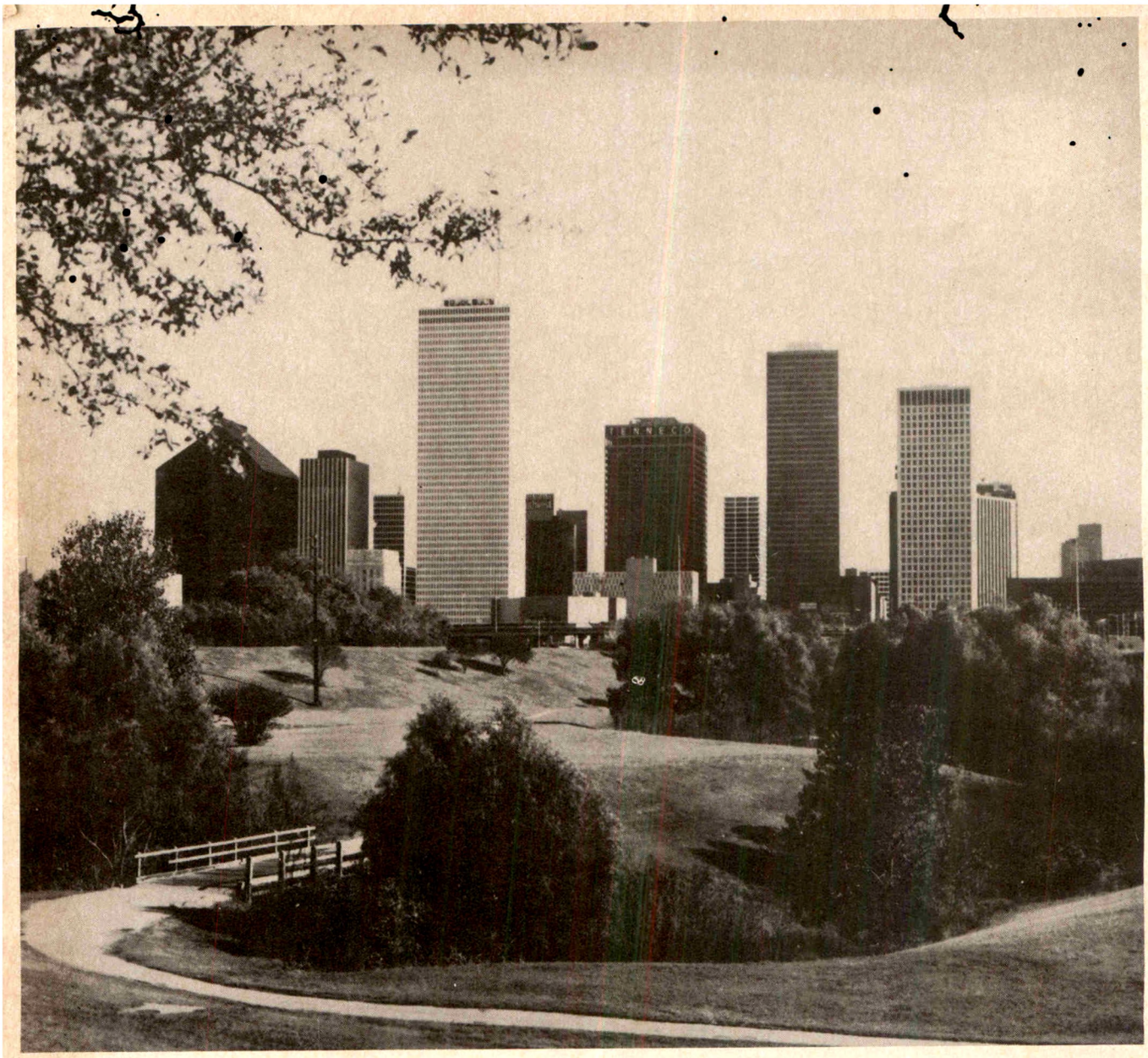

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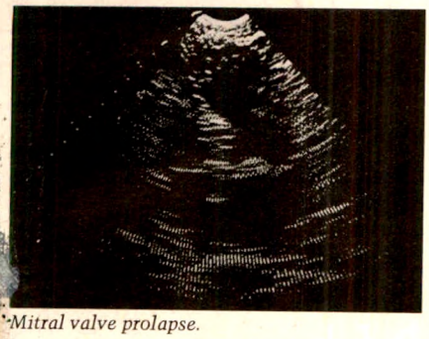
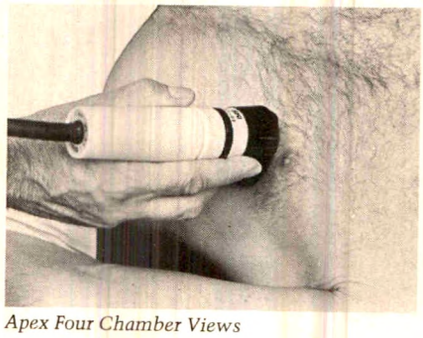


Mitral valve prolapse.



Apex Four Chamber Views

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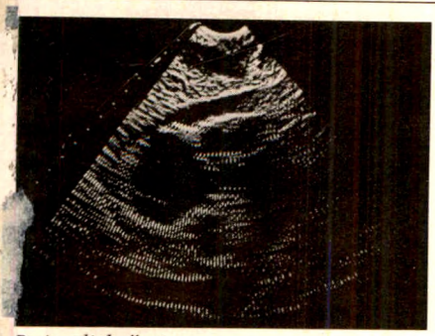
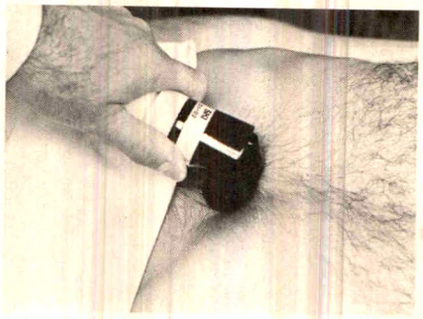
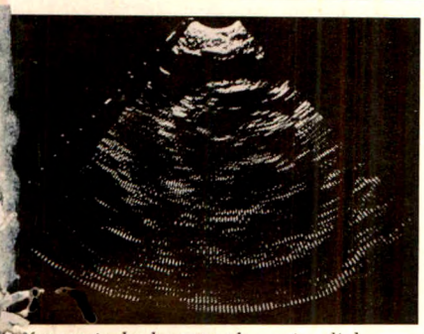


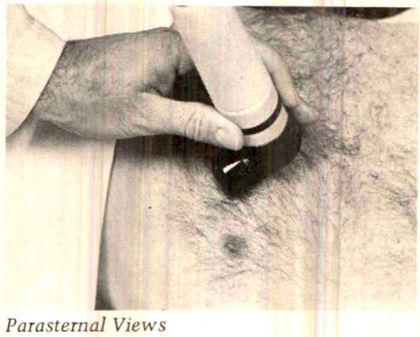
Pericardial effusion.



Subxyphoid Views



Left ventricular hypertrophy pericardial effusion, short axis.



Parasternal Views

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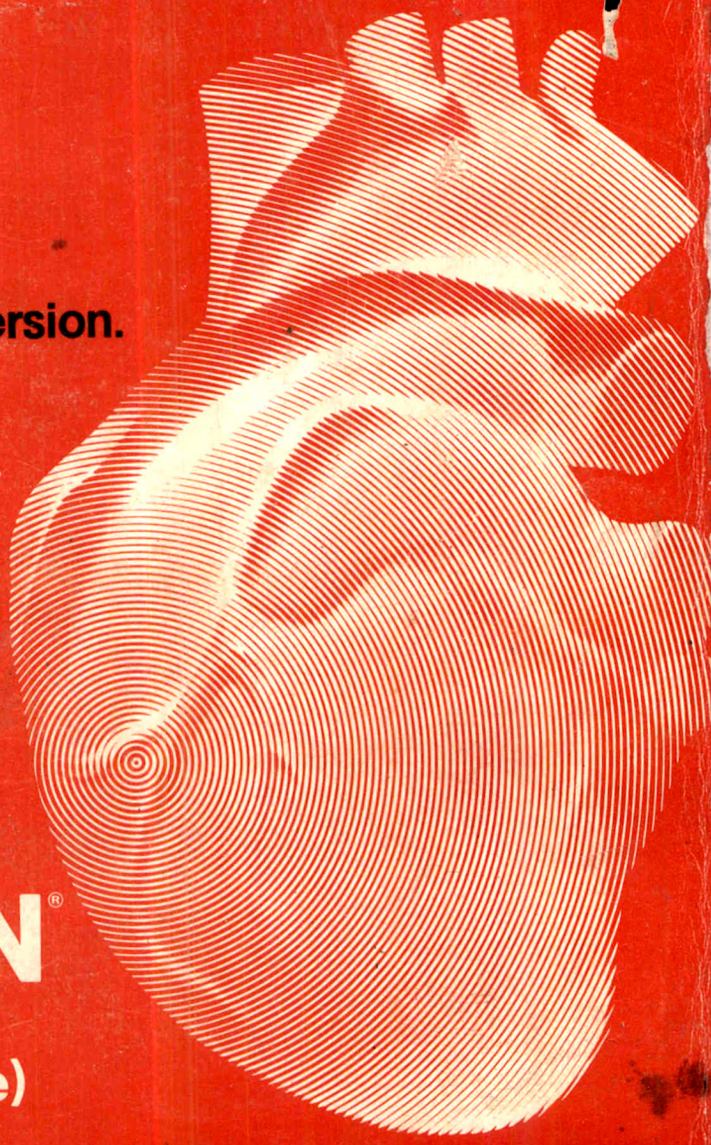

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- ☐ Greater GI tolerance than with quinidine sulfate
- ☐ Full quinidine cardiodynamics
- ☐ Convenient b.i.d. or t.i.d. dosage for most patients

CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of a broad range of cardiac arrhythmias (see Brief Summary). After conversion to normal sinus rhythm—whether with CARDIOQUIN Tablets or electroconversion—only low b.i.d. or t.i.d. dosage of this unique polygalacturonate salt of quinidine is required for maintenance in most cases. The polygalacturonic acid serves as a buffering moiety. It protects the mucosa of the stomach and permits dependable absorption of the quinidine.*

*Aviado, D. M., Krantz and Carr's Pharmacologic Principles of Medical Practice, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heart-block; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 100.

Purdue Frederick

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